NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Contents:

The following documents are made available to consultees and commentators

The **Final Scope** **and** **Final Matrix** are available on the NICE website.

1. **Company submission** from Astrazeneca UK

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   - Childhood Tumour Trust
   - British Paediatric Neurology Association (BPNA)
   - NHS England

4. **Expert personal perspectives** from:
   a. Dr Karine Lascelles – clinical expert, nominated by British Paediatric Neurology Association (BPNA)
   b. Mrs Clare Barklam – patient expert, nominated by Childhood Tumour Trust
   c. Ms Vanessa Martin - patient expert, nominated by Childhood Tumour Trust
   d. Dr Grace Vassallo – clinical expert, nominated by Astrazeneca

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews Ltd

6. **Evidence Review Group report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Selumetinib for treating symptomatic, inoperable plexiform neurofibromas (PN) associated with type 1 neurofibromatosis (NF1) in children aged 3 years and over [ID1590]

Submission of Evidence by AstraZeneca UK Limited

August 2021

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Glossary of terms

Term	Definition
Best objective response (BOR)	BOR was defined as the best response recorded from the start of treatment until progression or the last evaluable volumetric MRI assessment in the absence of progression
Complete response (CR)	CR was defined as the disappearance of the target PN
Confirmed partial response (cPR)	cPR was a PR observed on consecutive restaging examinations at least 3 months apart
Inoperable plexiform neurofibroma (PN)	Inoperable PN were defined as those which could not be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity. PN may only be considered operable in clinical practice if they can be completely surgically resected without risk of substantial morbidity; PN for which only partial resection can be achieved would therefore be considered inoperable
Neurofibromatosis type 1 (NF1)	A rare, complex and heterogenous genetic disease in which symptoms arise in early childhood and are lifelong. Clinical manifestations of NF1 can affect a wide range of organ systems and include a range of tumours associated with the nervous system
NF1 PN	Patients with NF1 may develop complex, non-malignant tumours of the peripheral nerve sheath called plexiform neurofibroma (PN); the presence of PN in patients with NF1 is referred to as NF1 PN
Objective response rate (ORR)	ORR was the percentage of patients with CR or cPR in an intention to treat analysis
Progressive disease (PD)	In the SPRINT Phase II trial, progressive disease was defined as an increase in volume of the target PN of ≥20% compared with baseline or, an increase of ≥20% from best response if a patient had had a PR
Partial response (PR)	In the SPRINT Phase II trial, a PR was defined as a decrease in the volume of the target PN by ≥20% compared with baseline
Partially resectable	PN which can be partly removed by surgery, with the proximity to critical structures often limiting the extent of removal
Symptomatic PN	In the SPRINT Phase II Stratum I, symptomatic PN were defined as PN causing significant morbidity including (but not limited to) head and neck PN which could compromise the airway, PN which could cause nerve progression, PN that could result in major deformity or are significantly disfiguring, PN causing limb hypertrophy or loss of function and PN causing pain
Unconfirmed partial response (uPR)	In the SPRINT Phase II trial, a PR was considered unconfirmed (uPR) at its first detection

Executive summary

Nature of the condition

Disease background

Neurofibromatosis type 1 (NF1) is a rare, complex, and incurable genetic disease which manifests as benign tumours throughout the body; symptoms arise in early childhood and continue into adulthood.[1] NF1 is highly heterogeneous, and can involve multiple organ systems (see Section 6.1).[2-5] Approximately 25% of patients with NF1 will develop non-malignant nerve sheath tumours called plexiform neurofibroma (PN);[6, 7] cases of NF1 in which PN are present are referred to as NF1 PN.

PN are heterogenous, can affect multiple body regions and can reach volumes of over four litres,[8-11] resulting in varied and often severe consequences as they obstruct/impact normal tissue function in the body. The majority of PN are symptomatic, and are associated with morbidities including:

- **Pain**, ranging from minor sensory alteration to severe, treatment resistant neuropathic pain
- **Difficulties with physical functioning**, airways, and vision (see Section 6.1).[9, 12, 13] In the most serious cases, PN can lead to significant disability, for example by placing pressure on spinal nerves and obstructing airways.[9, 14, 15] The spectrum of disease burden in patients with NF1 PN is wide-ranging, dependent on the size and location of the PN.
- **Disfigurement**, most notably of the face and neck, which can have a particularly large impact on emotional wellbeing and social functioning

PN growth

Paediatric patients with NF1 PN experience uncontrolled and unpredictable growth of PN, with periods of rapid growth followed by periods of tumour inactivity (see Section 6.1);[2, 11] a negative correlation is observed between patient age and growth rate.[16, 17] PN grow most rapidly in children <18 years old, with the fastest growth rates occurring in children aged <5 years old; increases in volume may reach ≥20% per year. Growth rates plateau into adulthood, with increases in volume of ≥20% per year rarely observed in patients aged ≥18.[16, 17] PN growth is also associated with increases in the number and severity of morbidities.[11, 18, 19] PN were rarely found to shrink spontaneously in the Natural History study and, as such, the burden of PN-associated morbidity will remain over a patient's childhood and adult life.[11, 17, 19]

In addition to the morbidity associated with PN, NF1 reduces patients' life expectancy (see Section 6.1). Due to the increased lifetime risk of developing certain forms of cancer, mortality rates are higher for NF1 patients than the general population.[20-23]

Impact of the disease on quality of life (Section 7)

NF1 PN has a substantial impact on the health related quality of life (HRQoL) of both patients and their parents and carers.[24, 25] Paediatric patients with NF1 PN reported

worse scores on eight of ten HRQoL domains, including meaning and purpose, depression, anxiety, psychological stress experiences, peer relationships, and physical function/mobility, when compared with the general population.[25]

PN-associated morbidities such as pain, disfigurement and motor dysfunction can have a considerable negative impact on patients' HRQoL, psychological health and wellbeing;[19, 25, 26] in particular, greater pain interference in everyday life is associated with increased depression, anxiety, socialisation difficulties and poorer overall HRQoL.[19] In addition, disfiguring PN can mean patients feel more self-conscious about their appearance, face isolation and bullying at school, impact patients' ability to participate in daily activities, and culminate in social isolation.[26, 27] This has a knock-on effect as patients reach adulthood, both in terms of their social and employment prospects.[28] With no active treatment option, patients face lifelong reductions in HRQoL with little hope of improvement.[11, 17, 19] Adult patients describe the interference of physical PN symptoms in their daily lives, a continued social and burden of visual disfigurement, and negative impacts of the disease on their careers.[28]

NF1 PN also has a detrimental impact on the daily lives and quality of life (QoL) of families and carers. Parents and carers of paediatric patients with NF1 PN describe providing support with: managing patient symptoms, aiding with daily activities, helping minimise disruption to education.[27] This support often extends into adulthood.[28] The uncertainty surrounding (potentially sudden) PN growth and PN-associated morbidities can be a constant source of anxiety for families and carers[14, 27] and caring duties can lead to missed working hours and productivity loss.[29]

Extent and nature of current treatment options (Section 8)

NF1 PN are typically identified by annual routine physical examinations or magnetic resonance imaging (MRI).[11, 30] Patients may have multiple PN, which need to be routinely monitored to determine which will become symptomatic (i.e. become associated with morbidity).

The only current management option to reduce or remove PN is surgery.[9, 31] However, as PN are large and invasive, surgery will often present unacceptable risk of morbidity. PN which have not been completely removed, especially those located in the head, neck and thorax, can regrow and continue to cause morbidities; even PN which have been completely resected can recur in paediatric patients.[9, 12, 32] Therefore, the term 'inoperable' is used to describe PN which cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity.[32] Approximately half of all patients with NF1 PN are considered inoperable.[9, 12, 31]

There are currently no available or approved pharmacological treatments to cure, prevent or reduce the volume of inoperable PN; patients must rely on symptomatic management only, ranging from pain medication to interventions such as tracheostomy to alleviate severe airway morbidities.[11, 19, 33]

As a result, there is a substantial unmet need for an effective treatment to stabilise and reduce PN volume, and manage the associated morbidities to give the chance for paediatric patients to lead a more 'normal' life.

Impact of the new technology

Selumetinib (Koselugo®) is the first licensed pharmacological treatment for NF1 PN that leads to significant reductions in PN volume and PN-associated morbidity, and has been shown to be tolerable in paediatric patients.[18, 34] Results from Stratum I of the SPRINT Phase II trial demonstrate that selumetinib treatment leads to significant and durable reductions and stabilisations in PN volume, accompanied by improvements in or without further worsening of PN-associated morbidities and patient HRQoL.[18, 34]

Therefore, selumetinib would represent a step-change in the management of NF1 PN.

Overview of the technology (Sections 2 and 3)

Selumetinib is a potent, selective, small molecule inhibitor of MEK1/2.[34, 35] MEK1/2 are key components of the RAS/RAF/MEK/ERK signalling cascade. By inhibiting MEK1/2,[35] selumetinib targets the underlying cause of PN growth, regulating abnormal cell proliferation and inducing cell death (Section 2.2). Selumetinib is the first technology licensed for this population (Section 3.2).

Selumetinib has received orphan drug designation[36] and conditional marketing authorisation from the European Medicines Agency (EMA) for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged three years and above.[37] [redacted]

Selumetinib is supplied as 10 mg and 25 mg hard capsules for oral administration, and is administered at a dose of 25 mg/m^2 body surface area (BSA), up to a maximum single dose of 50 mg, twice daily.

Methodology of relevant studies (Section 9.4)

The efficacy and safety of selumetinib has been assessed in the SPRINT Phase I/II clinical trial, a multicentre, open-label clinical study investigating selumetinib treatment in paediatric patients with NF1 with symptomatic inoperable PN.[18, 38, 39] Phase II Stratum I of the trial provides evidence for the target population for this submission, investigating selumetinib in paediatric patients with NF1 and symptomatic, inoperable PN.[38, 40]

The primary objective of Stratum I was to evaluate the confirmed partial and complete response rate of selumetinib using volumetric MRI analysis.[38, 40] In order to determine the comparative effectiveness of selumetinib vs established clinical management, non-randomised comparisons vs external control data were explored:[18, 34, 38]

- A naïve comparison between SPRINT Phase II Stratum I and an age-matched cohort of the NCI Natural History study[18]
- A naïve comparison of progression free survival (PFS) between SPRINT Phase II Stratum I and patients with progressive PN from the placebo arm of tipifarnib Study 01-C-02220222[41]

These external comparisons were planned as part of the protocol for SPRINT Phase II Stratum I.

Clinical effectiveness of selumetinib (Section 9.6)

SPRINT Phase II Stratum I recruited 50 patients with a median age of [redacted] years. The patients exhibited a range of PN sizes, locations and morbidities; median target PN volume was [redacted] and PN were associated with a median of [redacted] PN-related morbidities (Section 9.4.3):[34]

- The primary outcome of the SPRINT Phase II Stratum I study was objective response rate (ORR) (rate of confirmed partial response [cPR: ≥20% decrease in PN volume from baseline] and complete response [CR]) to selumetinib. The majority of NF1 PN patients receiving selumetinib in SPRINT Phase II Stratum I (68%) experienced a cPR These data contrast strongly with the results of the Natural History study, where no patients in the age-matched cohort showed a ≥20% reduction in PN volume.[18]

- Furthermore, patients receiving selumetinib in the SPRINT trial had a substantially higher probability of PFS at three years compared with the Natural History study age-matched cohort (84% vs 15%), demonstrating the stabilisation of patients' PN in the SPRINT trial vs the Natural History trial.[18] Children receiving selumetinib in the SPRINT trial also had a higher probability of PFS at two years compared to patients receiving placebo in the tipifarnib study [redacted].[34]

    - To confirm the comparability of the SPRINT and Natural History study populations, four different methods of propensity score adjusted analysis were performed (see Section 9.8.1); the results were robust to the choice of method and consistently support the benefit of selumetinib in reducing the risk of progression.

- Results from functional assessments of PN-associated morbidities demonstrate that selumetinib treatment improved functional outcomes (Section 9.6). Selumetinib treatment led to a clear reduction in pain intensity and selumetinib-treated patients and their parents further reported clinically meaningful improvements in PN-related pain interference with daily functioning. In addition, treatment with selumetinib results in clinically meaningful improvements in mobility, range of motion and strength for PN-associated body quadrants. Further benefits of selumetinib were seen with regards to improvements in airway functioning and disfigurement. The majority of patients [redacted] reported some degree of improvement in at least one PN-associated morbidity following selumetinib treatment.[34]

- Clinical improvements with selumetinib treatment were accompanied by a positive impact on patients' everyday lives, demonstrated through improved HRQoL. Based on self-reported Pediatric Quality of Life Inventory (PedsQL^{TM}) total scores, [redacted] patients showed a clinically meaningful improvement in HRQoL. Based on parent-reported PedsQL total scores, [redacted] patients showed an improvement in HRQoL. Improvements in both self- and parent-reported PedsQL scores were maintained through to pre-Cycle 25.[34]

Safety profile of selumetinib (Section 9.7)

Selumetinib monotherapy has a generally predictable and manageable safety profile in paediatric patients with NF1 PN. AEs were usually mild or moderate in severity. The most commonly reported AEs of any grade (≥70% of patients) were vomiting ([redacted] patients), blood creatine phosphokinase (CPK) increased ([redacted] patients) and diarrhoea ([redacted] patients).[18, 34, 42] AEs could generally be managed using dose interruptions or symptomatic/supportive care, rather than through treatment discontinuation, and subsequently resolved. No irreversible or cumulative toxic effects were observed; in total, only [redacted] discontinued treatment due to AEs.[18, 42]

Summary of health benefits of selumetinib (Section 9.9)

Overall, these data show that selumetinib offers significant clinical benefits to paediatric patients by inhibiting PN volume growth and preventing disease progression. These clinical benefits are mirrored by improvements in patients' HRQoL. Given that PN growth would otherwise occur at its greatest rate during childhood, it is expected that selumetinib will provide long-term durable benefits to patients into adulthood. Selumetinib addresses a substantial unmet need in this patient population, and allows patients to live a more normal life.[18, 34, 42]

Value for money

Summary of the cost-effectiveness analysis (Section 12)

If reimbursed in the UK, selumetinib will be the first active treatment available resulting in a step-change in the disease management for this patient population, where the disease burden is high for both paediatric patients with symptomatic inoperable NF1 PN, as well as their parents and families.

To our knowledge, this submission presents the first cost-effectiveness analysis for patients with NF1 PN. Due to limited availability of data, model structures such as full Markov state-transition and patient-level simulation models that are used across other disease areas were unfeasible, and a simplified AUC model structure was required. The model developed for this submission reflects the natural disease impact of NF1 PN on HRQoL and considers the potential lifetime benefit associated with selumetinib through reducing and stabilising tumour volume and PN growth, extended PFS, and improving patients' quality of life. Additionally, to address the evidence gaps around utility values, we conducted a novel TTO study specifically aimed at eliciting appropriate utility values in NF1 PN. The overall approach, underlying clinical rationale and key assumptions behind the economic model were validated by clinical experts in NF1 PN (Section 10.6.2 and 12.1).[28]

Selumetinib represents a cost-effective use of NHS resources with an estimated ICER of £93,169 per QALY versus current clinical management, which is below the £100,000 per QALY willingness-to-pay threshold for highly specialised technologies. Selumetinib is expected to provide an additional [redacted] QALYs versus current clinical management, which is consistent with the benefit of associated lifelong impact of preventing PN growth from childhood, where PN volume growth has been observed to be most rapid. These benefits are associated with an incremental cost of [redacted]. The robustness of the cost-effectiveness results was demonstrated through extensive scenario and sensitivity analyses, which showed good consistency with the base case ICERs.

Cost to NHS and personal social services

An estimated 37 patients would be eligible for treatment with selumetinib within the EMA label (Section 13.1). Over the next five years, [redacted] to [redacted] patients per year are estimated to be receive treatment with selumetinib, accounting for the anticipated uptake rates of selumetinib. Once accounting for treatment discontinuation, there would be an estimated [redacted] patients remaining on treatment in the first year rising to [redacted] patients in the fifth year.

The total cost to NHS England in the first year of selumetinib is estimated to be [redacted] in the first year, and [redacted] in the fifth year, which is far below the £20 million threshold required for the budget impact test

Impact of the technology beyond direct health benefits

A substantial proportion of the anticipated benefits of selumetinib are associated with improvements in HRQoL for both patients and their parents/carers. The reductions in PN-associated morbidities (including disability, pain and disfigurement) which result from selumetinib treatment, can benefit patients through improving their ability to perform normal activities of daily living, social functioning and emotional wellbeing. Parents/carers are also likely to experience HRQoL benefits as a result of the HRQoL improvements experienced by their child.[18, 19, 25, 26, 34, 43]

Selumetinib is also anticipated to bring cost savings to government bodies outside of the NHS and personal social services. Lifelong reductions in the degree of disability faced by patients and improved parent/carer productivity are anticipated to reduce the degree of financial support needed by families. Cost savings may also arise for the education system, from a reduction in the educational support required for children, as a result of fewer school days being missed for treatment.

Selumetinib will also have a positive impact on research and innovation. As the first licenced treatment for NF1 PN, selumetinib will provide an opportunity to understand the long-term impact of the treatment of these patients with a disease-modifying therapy, opening the door for further innovations in this patient population.

No additional infrastructure beyond that already in place within the NHS will be required for the effective use of and equitable access to selumetinib for all eligible patients.

Conclusion

Selumetinib represents a step-change in the management of paediatric patients with symptomatic, inoperable NF1 PN, for whom no disease-modifying treatments currently exist. Selumetinib treatment results in durable reductions in PN volume in paediatric patients, preventing or reducing the most rapid stage of PN volume growth. The stabilisation of and improvement in PN volume with selumetinib treatment leads to corresponding reductions in PN-associated morbidity and HRQoL improvement for paediatric patients, when compared to established clinical management. Treating paediatric patients with selumetinib, when their PN would otherwise be growing at their fastest rate,[11] represents an optimal pharmacological intervention to facilitate long-term disease control for patients.

Treatment with selumetinib represents a cost-effective option for NHS resources (with an ICER of £93,169) and an invaluable option for patients with symptomatic, inoperable NF1 PN. The eligible population for selumetinib treatment is small and well-defined, resulting in a low budget impact.

Section A – Decision problem

Summary of Section A

- Selumetinib (Koselugo®) is the first technology licensed for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged three years and above[37]

- NF1 is caused by mutations in the NF1 tumour suppressor gene, a negative regulator of RAS.[44-47] Loss of NF1 function results in increased cell proliferation and cell survival due to overactivation of the RAS/RAF/MEK/ERK growth factor signalling pathway. Increased cell proliferation and survival as a result of NF1 mutations results in the growth of PN[48-50]

- PN are complex, non-malignant peripheral nerve sheath tumours, which can occur anywhere in the body and cause substantial morbidities.[11] Selumetinib is a MEK1/2 inhibitor, targeting the underlying cause of PN growth by selectively inhibiting the RAS/RAF/MEK/ERK signalling cascade to regulate abnormal cell proliferation and induce tumour cell death[34, 35]

- Selumetinib is supplied as 10 mg and 25 mg hard capsules, to be administered orally. Selumetinib is administered at a dose of 25 mg/m2 BSA twice per day (BID), up to a maximum single dose of 50 mg[37]

- The efficacy and safety of selumetinib has been assessed in the SPRINT Phase I/II clinical trial, a multicentre, open-label clinical study investigating selumetinib treatment in paediatric patients with NF1 with inoperable PN (referred to as NF1 PN)[18, 38, 39]

    - Inoperable PN were defined as those that could not be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity[38]

- The SPRINT Phase I trial was a dose-escalation study which examined the maximum tolerated dose and pharmacokinetics of selumetinib in paediatric patients with inoperable PN which have the potential to become symptomatic[39]

- Phase II of the SPRINT trial was designed to evaluate the efficacy, safety and tolerability of selumetinib treatment in two patient populations:

    - Stratum I includes paediatric patients with symptomatic, inoperable PN; follow-up of these patients is ongoing. 50 patients were enrolled in this stratum, with data available for three years of follow-up.[18] This submission focusses on data from patients who were treated in this stratum, as the patient population aligns with the marketing authorisation for selumetinib

    - Stratum II includes paediatric patients with inoperable PN which have the potential to become symptomatic; this stratum is ongoing.[38] This stratum

falls outside the license for selumetinib and there is currently no regulatory plan for this indication

- The relative effectiveness of selumetinib has been investigated in comparative analyses of SPRINT Phase II Stratum I data with data from the NCI Natural History Study and the placebo arm of tipifarnib Study 01-C-0222[18, 34]

- NF1 affects males and females of all races and ethnic groups equally.[51] Currently, there are no available or approved, disease-modifying treatments for patients with NF1 PN, a population who will experience considerable morbidity and increased risk of a range of disabilities

1 Statement of the decision problem

Table A1. Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale for variation from scope
Population	Children aged three years and over with symptomatic and inoperable PN associated with NF1	Children aged three years and over with symptomatic and inoperable PN associated with NF1	N/A
Intervention	Selumetinib	Selumetinib	N/A
Comparator(s)	Established clinical management without selumetinib	Established clinical management without selumetinib, including pain management (prescription and over-the-counter painkillers)	N/A
Outcomes	• Complete and partial response rate • Growth rate of PN • Disfigurement • Physical functioning • Visual function • Airway functioning • Bowel and bladder continence • Pain • Adverse effects of treatment • HRQoL (children)	In addition to those detailed in the final scope, the following relevant outcomes will be presented: • Duration of response • PFS • Time to progression • Global impression of change	Additional outcomes from the SPRINT Phase II Stratum I trial (duration of response, progression free survival, time to progression and global impression of change) are relevant for assessing the efficacy of selumetinib
Cost to the NHS and PSS, and Value for Money	• Cost-effectiveness expressed in terms of incremental cost per QALY • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs should be considered from an	The economic analysis has been conducted in line with the NICE reference case	N/A

	NHS and PSS perspective		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service[a]	• Whether there are significant non-health benefits • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Additional staffing and infrastructure requirements, including training and planning for expertise	All points have been considered within this submission	N/A
Special considerations, including issues related to equality	No special considerations identified	No special considerations identified (see Section 5)	N/A

Footnotes: [a]Details of the impact of selumetinib beyond direct health benefits and on the delivery of the specialised service have been reported in Section E as per the submission template.

Abbreviations: HRQoL: health-related quality of life; N/A: not applicable; NHS: National Health Service; NF1: type 1 neurofibromatosis; PFS: progression free survival; PN: plexiform neurofibromas; PSS: personal social services; QALY: quality adjusted life year.

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand Name: Koselugo®

Approved generic name: Selumetinib

Therapeutic class/ATC code: L01EE04

2.2 What is the principal mechanism of action of the technology?

Selumetinib is a potent, selective, small molecule inhibitor of MEK1/2[34, 35] indicated for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged three years and above.[37]

NF1 is caused by mutations in the *NF1* tumour suppressor gene, a gene most highly expressed in the nervous system. The *NF1* gene produces the protein neurofibromin, which is required for the negative regulation of the RAS/RAF/MEK/ERK growth factor signalling cascade. Loss of *NF1* function, and therefore functional neurofibromin protein, leads to elevated RAS/RAF/MEK/ERK activation, resulting in abnormal cell proliferation and cell survival.[48-50, 52-54]

NF1 is a highly heterogeneous disease with a number of different manifestations (as described in Section 6.1) and it is unclear how many of the symptoms result from the underlying genetic mutation.[54] However, the association between loss of *NF1* function and the development of tumours, including PN, is well understood. PN are complex peripheral nerve sheath tumours composed of multiple cell types. Loss of functional neurofibromin leads to abnormal cell proliferation and survival in the peripheral nerve sheaths, leading to the development and uncontrolled growth of PN.[55-57]

Selumetinib inhibits MEK1/2,[35] key components of the RAS/RAF/MEK/ERK signalling cascade, thus preventing PN growth and promoting PN shrinkage by reducing cell proliferation and preventing abnormal cell survival.

2.2.1 Please complete the table below.

Table A2. Dosing Information of technology being evaluated

Pharmaceutical formulation	Selumetinib is supplied as 10 mg and 25 mg hard capsules
Method of administration	Selumetinib is an oral medicine.
Doses	Selumetinib is administered at a dose of 25 mg/m^2 BSA, up to a maximum single dose of 50 mg. The dosing scheme for selumetinib is presented in Table A3
Dosing frequency	Selumetinib capsules are administered BID (approximately every 12 hours)
Average length of a course of treatment	Paediatric patients can start selumetinib treatment following NF1 diagnosis and the identification of symptomatic, inoperable PN. Treatment with selumetinib should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. In SPRINT Phase II Stratum I, the median total duration of treatment with selumetinib at data cut-off 29th March 2019 (3 years of follow-up) was approximately 2.5 years (892.7 days).[58]
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	The dose of selumetinib is reduced following the development of defined toxicities; recommended dose reductions are given in SmPC, based on patient BSA and grade of AE. Selumetinib dosing should also be adjusted to account for patient growth

Abbreviations: AE: adverse event; BID: twice daily; BSA: body surface area; N/A: not applicable; NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas; SmPC: summary of product characteristics.
Source: AstraZeneca Data on File (Selumetinib Summary of Product Characteristics)[37]

Table A3. Dosing scheme for selumetinib 25 mg/m^2 BID

BSA (m^2)	Dose (mg)
0.55–0.69	20 mg morning dose 10 mg evening dose
0.70–0.89	20 BID
0.90–1.09	25 BID
1.10–1.29	30 BID
1.30–1.49	35 BID
1.50–1.69	40 BID
1.70–1.89	45 BID
≥1.90	50 BID

Abbreviations: BID: twice per day; BSA: body surface area.
Source: AstraZeneca Data on File (Selumetinib Summary of Product Characteristics)[37]

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Selumetinib was granted orphan drug designation by the EMA in July 2018.[36] The EMA marketing authorisation application for selumetinib was filed in March 2020.[59] Positive EMA Committee for Medicinal Products for Human Use (CHMP) opinion was received in April 2021, recommending the granting of a conditional marketing authorisation for selumetinib[60, 61] and conditional marketing authorisation was received in June 2021.[62] Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation of selumetinib will occur through the European Commission decision reliance route and is expected in August 2021.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that selumetinib will be commercially available in the UK upon regulatory approval and the subsequent NICE appraisal process. Selumetinib is currently being offered to UK patients as part of the selumetinib Early Access Program (EAP), with [redacted] patients in England currently receiving selumetinib through the scheme.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Positive EMA CHMP opinion was received in April 2021, recommending the granting of a conditional marketing authorisation for selumetinib.[60, 61] Selumetinib received conditional marketing authorisation in June 2021.[62]

Selumetinib has regulatory approval in the United States of America (Food and Drug Administration [FDA] approval),[63] where it also has an orphan drug designation and breakthrough therapy designation. In the United States selumetinib is indicated for the treatment of paediatric patients two years of age and older with NF1 who have symptomatic, inoperable PN.[64, 65] Selumetinib has also been granted regulatory approval in Brazil, Israel, Singapore, South Korea and the United Arab Emirates.

3.3.1 If the technology has been launched in the UK provide information on the use in England.

Not applicable.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

SPRINT (NCT01362803) is the pivotal study for selumetinib in paediatric NF1 patients with inoperable PN and is currently ongoing. SPRINT is a Phase I/II, multicentre, open-label clinical trial examining the efficacy, safety and tolerability of selumetinib for the treatment of PN in paediatric NF1 patients.[18, 38] Inoperable PN were defined as those that cannot be surgically removed without risk of substantial morbidity due to encasement of or close proximity to viral structures, invasiveness, or high vascularity (see Section 8 for further information on current management options for NF1 PN).[38]

Phase I of the SPRINT trial was a dose-escalation study designed to determine the maximum tolerated dose and evaluate the pharmacokinetics of selumetinib in paediatric patients with inoperable PN which have the potential to become symptomatic. Trial results indicated that patients were able to receive selumetinib on a long-term basis with a maximum tolerated dose of 25 mg/m^2. A confirmed partial response (cPR, tumour volume decrease from baseline of ≥20%) was observed in 17 of 24 children (71% of patients), with a median change in tumour volume of 31%.[39] Follow-up of some patients is ongoing; nine patients remained on treatment at the most recent data cut-off (DCO; 27th February 2021).[66]

The SPRINT Phase II trial was designed to evaluate the response rate to, and clinical benefit of, selumetinib treatment and included two strata, with the following inclusion criteria:

- Stratum I included patients aged 2–18 with NF1 and symptomatic, inoperable PN (broadly in line with the anticipated licence for selumetinib and the decision problem for this evidence submission)

- Stratum II included patients aged 2–18 with NF1 and inoperable PN which have the potential to become symptomatic (this stratum falls outside the license for selumetinib and there is currently no regulatory plan for this indication)

Follow-up on patients enrolled in both strata is ongoing. Further details on SPRINT Phase II Stratum I are provided in Section 9.6.

In addition to the SPRINT trial, results from a number of real-world studies investigating experiences of selumetinib in the relevant population have been published. These studies are outlined in Section 9.3.

Table A4. Overview of ongoing clinical studies of selumetinib in paediatric NF1 PN

Study name/number	Design	Patient population	Selumetinib dose(s)	Outcome measures	Total number of patients	Status
SPRINT Phase I/II trial (NCT01362803)[18, 38, 39, 67]	Phase I, open-label	Patients aged 3–18 with NF1 and inoperable PN which have the potential to become symptomatic	20–30 mg/m^2 BSA BID	• Maximum tolerated dose • Pharmacokinetics • Response (increase or decrease from baseline in the volume of PN)	24	Results available[39, 66]
	Phase II, open-label	**Stratum I**: patients aged 2–18 with NF1 and symptomatic, inoperable PN	25 mg/m^2 BSA BID	• ORR • DoR • PN growth rate • TTP and PFS • HRQoL • Safety and tolerability	Stratum I: 50	Ongoing (results available, see Section C 9.4)[18]
		Stratum II: patients aged 2–18 with NF1 and inoperable PN which have the potential to become symptomatic	25 mg/m^2 BSA BID	• ORR • DoR • PN growth rate • TTP and PFS • HRQoL • Safety and tolerability	Stratum II: 25	Ongoing, results available[68]

Abbreviations: BID: twice per day; BSA: body surface area; DoR: duration of response; HRQoL: health-related quality of life; NF1: type 1 neurofibromatosis; ORR: overall response rate; PFS: progression free survival; PN: plexiform neurofibromas; TTP: time to progression.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

[redacted].

5 Equality

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

NF1 affects male and female patients in equal numbers; it also affects all races and ethnic groups equally.[51]

No issues relating to equity or equality that are relevant to this submission have been identified, other than the fact that NF1 PN is a rare and incurable genetic condition. At present there is no licensed treatment for this patient population (Section 8.2) who will experience considerable morbidity and increased risk of a range of disabilities (Section 7.1).

Individuals with NF1, including those with NF1 PN, have increased risk of cognitive impairments and learning disabilities.[2, 69, 70] Most patients with NF1 PN suffer from a range of disabilities and morbidity; in the most serious cases, PN can lead to significant disability (for example by placing pressure on spinal nerves and obstructing airways) or life-threatening organ impairment.[9, 14, 15] Treatment with selumetinib has been shown to improve HRQoL and reduce PN-associated morbidity in paediatric patients, thus reducing the burden of disease for patients with cognitive and physical disabilities.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

- **NF1 is a rare, complex, lifelong and incurable genetic disease**, with many symptoms arising in early childhood and continuing into adulthood.[1] As a genetic, heritable condition, multiple members of a family may be affected.[1] NF1 is a highly heterogeneous disease that can express differently between patients, and even between family members with identical mutations[71-74]

- **Approximately 25% of NF1 patients develop non-malignant nerve sheath tumours called PN** (referred to as NF1 PN).[6, 7] PN are heterogenous, and can affect multiple body regions and reach extremely large volumes of over four litres,[8-11] resulting in varied and often severe consequences

- **The majority of PN are symptomatic, and are associated with morbidities such as pain, disfigurement and difficulties with physical functioning**.[9, 11-13] In the most serious cases, PN can lead to significant disability or life-threatening organ impairment, for example by placing pressure on spinal nerves and obstructing airways[9, 14, 15]

- **Children with NF1 PN experience uncontrolled and unpredictable growth of PN**, with periods of rapid growth followed by periods of slow or no growth.[2, 11]

    - A negative correlation has been observed between patient age and growth rate.[16, 17] PN grow most rapidly in children <18 years old, with increases in volume reaching ≥20% per year.

    - **Growth rates tend to plateau by adulthood**, with increases in volume of ≥20% per year rarely observed in adult patients.[16, 17]

- **PN growth is associated with increases in the number and severity of morbidities**.[11, 18, 19] As PN rarely shrink spontaneously, the burden of PN-associated morbidity will remain over a patient's entire lifetime[11, 17, 19]

- **PN-associated morbidities such as pain, disfigurement or motor dysfunction can have a substantial negative impact on patients' physical health and daily functioning**.[19, 25, 26] In paediatric patients with NF1 PN there exists a considerable caregiving burden for parents, families and other carers[14, 75]

- **Currently, the only option for reducing PN volume and alleviating PN-associated morbidities is surgery**. However, surgery is accompanied by a high risk of complications and approximately half of NF1 PN patients are considered inoperable.[9, 12, 31] There is therefore an unmet need for an effective treatment to stabilise and reduce PN volume in order to manage the morbidities associated with PN

- Due to the increased lifetime risk of developing certain forms of cancer, mortality rates are higher for NF1 patients than the general population.[20-23] In addition, NF1 PN patients have

a higher mortality rate compared to the NF1 population, due to the increased risk of developing MPNSTs[76]

- The total patient population eligible for selumetinib in England has been calculated to be 37, based on statistics for the total size of the paediatric population in England,[77] the prevalence of NF1,[6] and the proportion of paediatric NF1 patients with symptomatic, inoperable PN[6, 7, 15, 78, 79]

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

This submission focusses on the paediatric NF1 PN population and presents data from paediatric patients wherever possible. Data from the adult population has only been presented where no paediatric data are available, or to provide evidence for the lifelong effects of the disease.

Neurofibromatosis type 1

NF1 is a rare, complex, lifelong and incurable genetic disease. As the condition is heritable,[1] multiple members of the same family may be affected. Many of the symptoms of NF1 arise in early childhood and continue into adulthood.[1] The majority of NF1 patients (80–85%) are diagnosed by the age of six, and 95% of NF1 patients are diagnosed by the age of eight years.[1, 80]

NF1 is a highly heterogeneous disease, that can express differently between patients, and even between family members with identical mutations.[71-74] NF1 can present a wide range of clinical manifestations involving multiple organ systems, with symptoms affecting the nervous system, skin, bones and eyes.[2-5] Individuals with NF1 have an increased risk of cognitive impairments, learning disabilities and mental health disorders.[2, 69, 70] NF1 patients also have an increased lifetime risk of developing certain forms of cancer, including MPNSTs, brain tumours, gastrointestinal stromal tumours, breast cancer and leukaemia.[21] For the majority of NF1 patients the clinical course of the disease is uncertain, which can be a source of anxiety for both patients and their families or carers.[1, 14, 75]

Plexiform neurofibroma

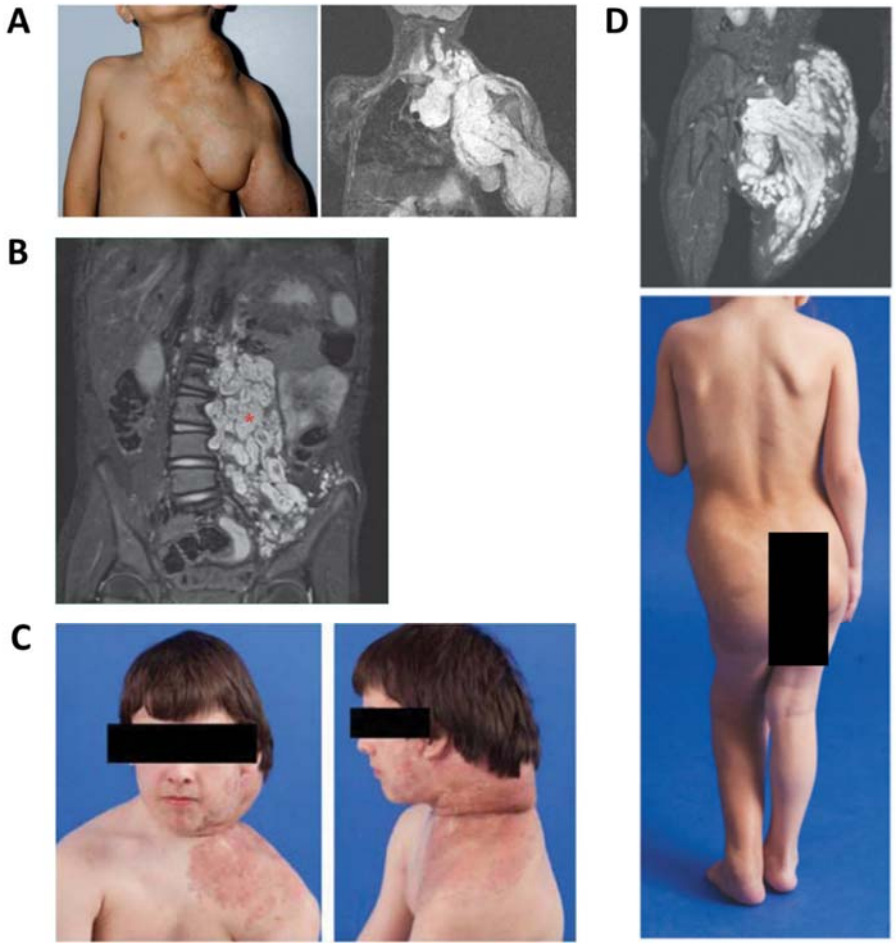
A feature of NF1, thought to occur in around 25% of patients, is the presence of PN.[56 8, 78] PN are non-malignant peripheral nerve sheath tumours, which can occur anywhere in the body and cause substantial morbidities, often due to their size and invasiveness.[11] PN may be confined and nodular, or involve multiple body regions, and most commonly occur in the paraspinal region (31%), head and neck (31%) and extremities (25%) (Figure B1).[8-10] PN can reach extremely large sizes, with tumours of over four litres in volume having been recorded in paediatric patients.[11] Once PN develop they are unlikely to resolve spontaneously, and therefore will persist throughout a patient's lifetime (see Section 6.1 Disease course).[11, 18]

The majority of PN are defined as symptomatic (see Glossary of terms), as they are typically associated with morbidities such as pain, disfigurement and difficulties with physical functioning.[9,

[11-13] Patients with symptomatic NF1 PN experience the morbidities associated with their PN (see Section 6.1 PN-associated morbidities) in addition to the clinical manifestations associated with NF1.

The only existing management option for PN which can reduce or remove the tumours is surgery.[9, 31] As PN are large and invasive they present many difficulties in terms of surgical resection. PN which have not been completely removed, especially those located in the head, neck and thorax, can regrow after surgery and continue to cause morbidities; even PN which have been completely resected may recur in paediatric patients.[9, 12, 32] Therefore, the term 'inoperable' is used to describe PN which cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity (see Glossary of terms and Section 8).[32] This definition of inoperability was used in the inclusion criteria for the SPRINT Phase I/II clinical trial of selumetinib in paediatric NF1 patients with inoperable PN, on the basis of which selumetinib has received a conditional EMA license. Approximately half of all patients with NF1 PN are considered inoperable.[15, 79]

Figure B1. Images showing a range of PN sizes, shapes and locations



Footnotes: PN show on MRI as white masses. A) Paediatric patient with NF1 and large PN extending over the chest neck and left arm. The photograph shows the extent of the external disfigurement that PN can cause. The corresponding MRI shows the internal invasion of the PN, and compression of surrounding organs and structures including the heart, airway and arm musculature.[81] B) An MRI of an extensive PN in the paraspinal region of an 8-year-old boy.[21] C) PN on the cervical spine (head and neck region) of a 14-year-old boy with NF1.[11] D) Photograph and corresponding MRI of PN on the trunk of a child with NF1.[39]
Abbreviations: MRI: magnetic resonance imaging; NF1: type 1 neurofibroma; PN: plexiform neurofibromas.

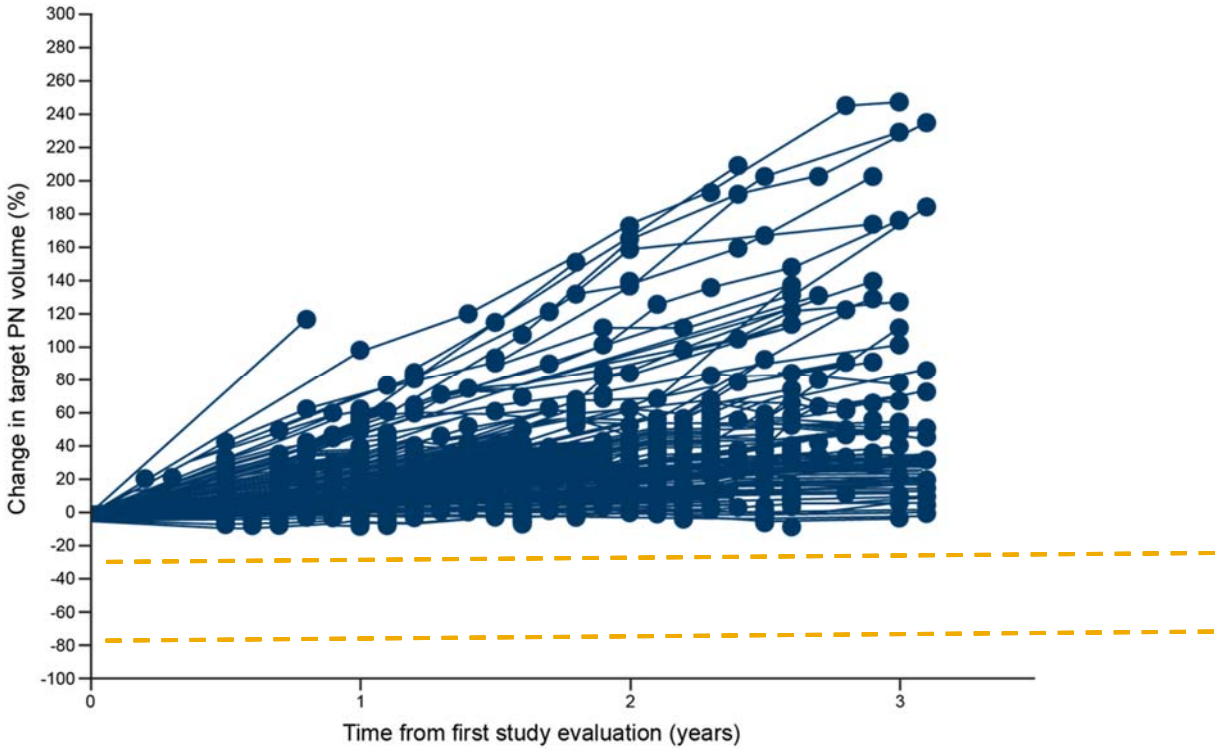
Source: Dagalakis et al. 2014;[81] Hirbe et al. 2014;[21] Gross et al. 2018;[11] Dombi et al. 2016.[39]

The most comprehensive study of the natural history of NF1 PN is the US NCI Natural History study of Patients with NF1 (NCT00924196), henceforward referred to as the Natural History study.[82] The Natural History study, which enrolled 157 patients in total (children and adults), is the first large, observational study to assess long-term changes in NF1 PN tumour volume and clinical morbidities. The study provides the best available data on the experiences of NF1 PN patients in current clinical practice; further details can be found in Section 9.4.

Disease course and PN growth

Children with NF1 PN experience uncontrolled and unpredictable growth of PN, with periods of rapid growth followed by periods of slow or no growth.[2, 11] The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria have been used in a number of NF1 PN clinical trials to define PN volume decrease and increase (often referred to as PN progression and improvement).[18, 83, 84] Under the REiNS criteria, PN volume increase is defined as a ≥20% increase in tumour volume from baseline and PN volume decrease is defined as a ≥20% decrease in tumour volume from baseline. In the Natural History study, 49/57 (86%) PN underwent a ≥20% increase in tumour volume between baseline and maximum assessment (median time between baseline and maximum assessment was 6.5 years [range 0.7–12.6 years]), with the median PN volume change from baseline being 109% (Figure B2).[11]

Figure B2. PN growth over time in an age-matched cohort[a] of patients included in the Natural History study



Footnotes: Dotted lines show a 20% increase and 20% decrease in PN volume; these thresholds represent the REiNS criteria definitions of PN volume increase and decrease, often interpreted as PN progression and clinical improvement in clinical trials. Volume changes of <20% per year being defined as stable disease.[18] [a]Patients from the Natural History study included in this cohort were age-matched to the patients included in the SPRINT Phase II Stratum I clinical trial over a matched duration of observation (3.2 years).
Abbreviations: PN: plexiform neurofibromas; REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis.

Source: Gross et al. 2020.[18]

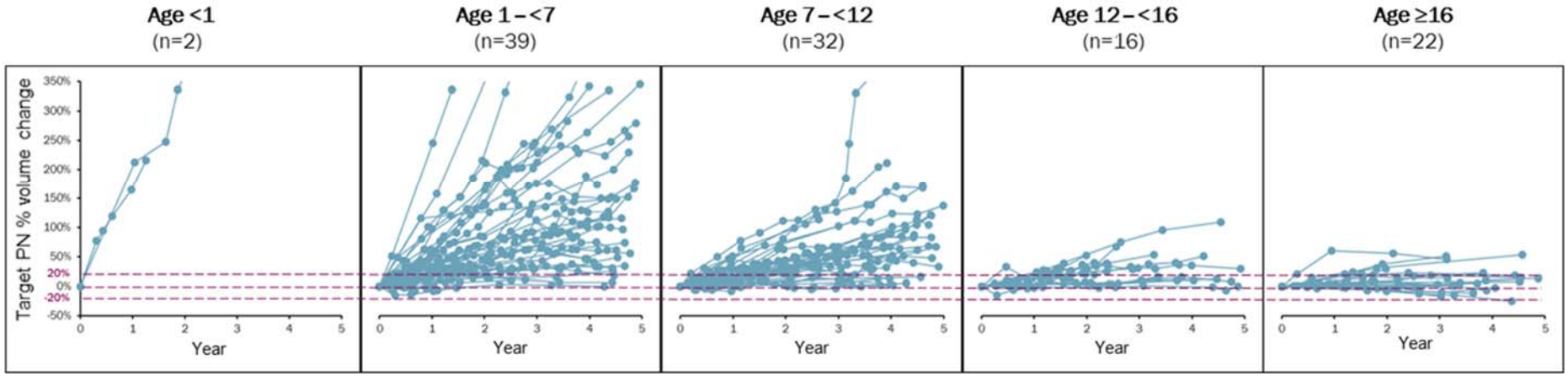
PN, especially those in paediatric patients, rarely decrease in volume spontaneously.[11, 18] In the Natural History study, few patients (10/113, 9%) experienced a spontaneous tumour volume reduction over the full follow-up period ([redacted] years). Only three of these patients were younger than 18 years of age.[17]

Growth rates of PN plateau into adulthood

PN growth rate varies but generally slows with age, as observed in the Natural History study.[16, 17] PN were found to grow most rapidly in children <18 years old, with the highest PN growth rates being observed in young children;[16, 17] patients aged 3–5 years experienced a median growth rate of 35% per year.[11] Young children therefore experience a rapid disease course, where PN may reach large sizes early in their lives. As shown in Figure B3, whilst the majority of patients experienced a ≥20% increase in PN volume in early childhood (ages 0−12), growth rates plateaued by 12–18 years of age.[85] Volume increases of ≥20% were rarely observed in adult Natural History study patients, [17] but patients will continue to experience the existing burden of PN-associated morbidities, resulting in poorer HRQoL.[11, 17, 19]

Given that PN growth rates are closely linked to age, and that PN rarely decrease in volume spontaneously, **preventing PN growth in early childhood would have a lifelong impact by preventing or reducing the most rapid stage of PN volume growth**. With PN growth associated with an increase in morbidity[11] (see Section 6.1 PN-associated morbidities), long-term reduction in PN volume is expected to result in a substantial reduction in the lifelong burden of disease.

Figure B3. Change in PN growth from NCI Natural History study individual patient profiles, over five years by age group



Abbreviations: PN: plexiform neurofibroma.
Source: AstraZeneca Data on File[85]

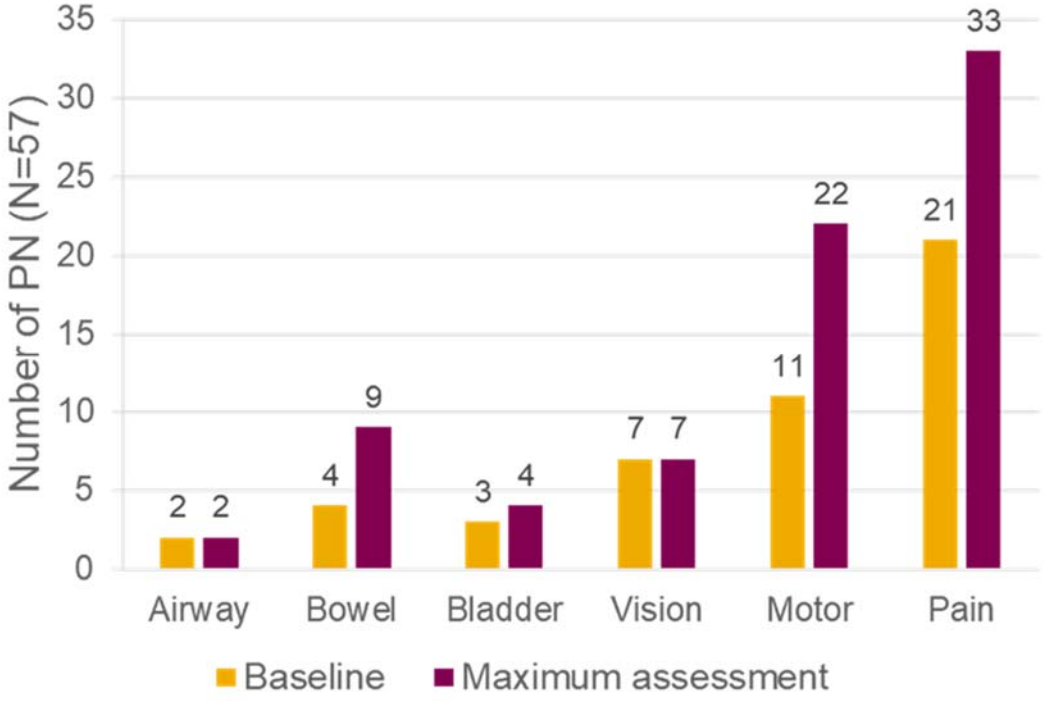
PN-associated morbidities

NF1 PN is a heterogenous condition: PN can affect multiple body regions and can reach extremely large sizes.[8-11] This resulting in varied and often severe morbidities including pain, motor dysfunction and disfigurement. In the Natural History study, the majority of PN (70%, 40/57 PN representing 88% of patients [36/41]) were associated with morbidities at baseline. Many of these PN were associated with multiple morbidities; 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline (Figure B4).[11]

Uncontrolled growth leads to an increasing burden of PN-associated morbidity over time. In the Natural History study, the number of associated morbidities increased for 30/57 (53%) of PN over time, including 8 PN which were not associated with a morbidity at baseline. No stable or growing PN had a resolution of associated functional morbidities between baseline and maximum assessment (the clinical assessment at which the PN reached its maximum volume); all morbidities present at baseline were also present at maximum assessment.[11]

As described above, with PN rarely shrinking spontaneously, in the absence of disease-modifying treatment the burden of PN-associated morbidity will remain over a patient's childhood and adult life.[11, 17, 19]

Figure B4. Number of PN with each type of PN-associated morbidity at baseline and maximum assessment



Footnotes: [a]'Maximum assessment' refers to the clinical assessment at which the PN reached its largest volume.
Abbreviation: PN: plexiform neurofibromas.
Source: Gross et al. 2018.[11]

Pain Morbidity

PN are a common source of neuropathic pain and neurologic dysfunction, ranging from minor sensory alteration to complete myelopathy.[8] Pain was identified as a PN-associated symptom in 30–41% of patients with PN across two studies, with pain resulting from contact with or pressure applied to the PN was the most commonly reported type of pain.[6, 70] Figure B4 shows that the most common PN-related morbidity in the Natural History study at baseline and maximum assessment was also pain. An increase in PN-associated pain was observed over time, with a concordant increase in pain medication usage.[11] More PN required more effective pain relief at maximum assessment than at baseline, with the use of scheduled, neuropathic and opioid pain medication tripling over this time period.[11]

PN-associated pain can be severe and difficult to manage: 20/60 (33%) patients in the Natural History study were taking pain medication regularly. Of these patients, including five children and 15 adolescents, 18/20 (90%) were taking prescription pain medications or a combination of over-the-counter and prescription pain medications.[19] Despite regular pain medication use, 14/15 (93%) of these adolescents and 20/20 (100%) of the carers reported that pain was still interfering with daily functioning to some degree.[19] Pain may also increase in intensity with physical activity.[27]

Motor Morbidities

PN restricting the range of motion of a joint or causing pain during movement may lead to impaired motor function in patients with NF1 PN. In serious cases, growing spinal and paraspinal neurofibromas can put pressure on spinal nerves, leading to significant muscle weakness and disability.[14]

In the Natural History study, the number of PN-related motor morbidities doubled from 11 to 22 between baseline and maximum assessment. The PN which contributed to motor dysfunction generally had larger volumes (median 818 mL) than those which did not (median 238 mL).[11] Therefore, growth of PN over time can lead to increasing severity of motor dysfunction.

Airway Morbidities

Studies beyond the Natural History study have shown that growth of PN near airways can lead to serious morbidities, including airway obstruction, which requires patients to undergo tracheostomies,[86] and in some cases leads to death.[9, 15] PN which compromise airways or cause pulmonary dysfunction are thought to occur in 5–7% of paediatric NF1 PN patients.[87] Airway PN can also cause morbidities such as sleep apnoea, which may be treated with continuous positive airway pressure.[33, 87]

Bladder and Bowel Morbidities

PN in the region of the bladder and bowel can impede the function of these organs, causing burdensome symptoms such as incontinence. Growth of these PN can result in more severe complications such as bowel obstruction or blood in the urine.[11, 28]

Vision Morbidities

PN involving the eyelid, orbit, periorbital and facial structures can cause significant visual loss, in some cases requiring enucleation (removal of the eye).[34] Growth of PN around the eye and eyelid can prevent the eye from achieving normal visual acuity (amblyopia), cause eye pain, drooping of the eyelid (ptosis) and severe protrusion of the eye (proptosis). Patients with orbital

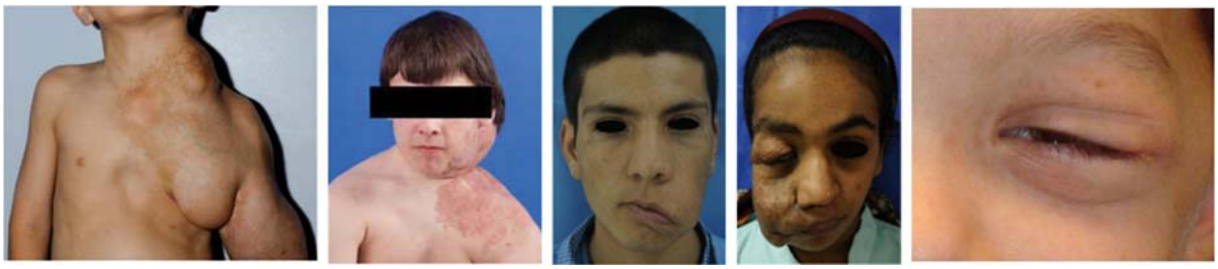
and periorbital PN are at risk of developing glaucoma and optic nerve disease due to compression, especially if the PN grows rapidly.[13]

Disfigurement

The growth and development of visible PN, such as those on the head and neck, can result in severe disfigurement (Figure B5). This is especially true of orbital and periorbital PN, where resulting ptosis, proptosis, cheek deformities and asymmetry of the eyelids can cause significant alterations in appearance.[13] In addition to the impact on appearance and as noted above, facial PN can contribute to functional morbidities such as vision loss.[13]

Beyond the Natural History study, studies have shown that disfiguring facial PN often develop during early life,[2] and can have a negative impact on social and physical functioning and self-esteem.[13, 26] In a study of clinical burden in paediatric NF1 PN patients in the US, 32.9% of patients had a disfiguring PN, and disfigurement was the second most common PN-associated morbidity.[88] In addition, adult NF1 PN patients in the UK reported the need to find clothes that were comfortable and that fit around their PN, in order to hide the appearance of the PN.[28] Further information on the impact of disfigurement on daily life and QoL is reported in Section 7.1.

Figure B5. Disfigurement of the upper body and face due to PN



Abbreviations: PN: plexiform neurofibromas.
Source: Avery et al. 2007;[13] Dagalakis et al. 2015;[81] Faryabi and Mehrabizadeh 2017;[89] Gross et al. 2018.[11]

Mortality in NF1 PN

In addition to PN-associated morbidities, NF1 PN impacts patients' life expectancy. Patients with NF1 have a higher mortality rate and lower life expectancy than the general population due to an increased lifetime risk of developing certain types of cancer.[20-23] Patients with NF1 PN have been shown to have a higher mortality rate than the general NF1 patient population; an increase in mortality rate of 3.2% has been observed in patients with NF1 and symptomatic PN, compared to NF1 patients with no PN or asymptomatic PN (p=0.024).[9] One reason for the increase in mortality observed in NF1 PN patients may be the development of malignant peripheral nerve tumours (MPNSTs). MPNSTs are thought to be associated with PN, with the risk of developing an MPNST being increased 20-fold in an area with an existing PN.[90] It is unclear whether treatment which reduces or removes PN modifies this risk.

Unmet need in NF1 PN

As described above (see Section 6.1), PN growth in children is uncontrolled and unpredictable,[2, 11, 16, 17] resulting in increases in the number and severity of morbidities over time and an increasing, lifelong burden on patients and their parents/carers.[11, 18, 19] Current management of symptomatic inoperable NF1 PN is palliative, and focussed on alleviating PN-associated morbidities, for example through the use of pain medications (see Section 8.2).[11, 19, 33] The only

option for reducing PN volume and alleviating PN-associated morbidities is surgery, however, surgery is accompanied by a high risk of complications. Many NF1 PN patients (approximately 50%) are considered inoperable.[15, 79]

Therefore, there exists a substantial unmet need for an effective treatment to stabilise or reduce PN volume in order to manage the morbidities associated with inoperable PN.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

The size of the population eligible for selumetinib treatment in England has been calculated at 37 patients (Table B1). This figure is based on detailed hospital episode statistics records using primary diagnosis codes for neurofibromatosis,[91] which is likely to slightly overestimate the number of patients with NF1 (given the additional patients with NF2 and schwannomatosis), and the proportion of paediatric NF1 patients with symptomatic, inoperable PN.

Table B1. Total eligible patient population for selumetinib in England

Population	Estimated proportion	Estimated number	Source
Total population aged 3–17 years in England	-	10,140,338	Office for National Statistics, mid-2020[77]
Total number of admissions of neurofibromatosis (aged 3-17)	-	538	Hospital Episode Statistics - Primary diagnosis: 4-character table, neurofibromatosis (non-malignant) Q85.0, 2019-2020; assumed mostly NF1[91]
Proportion of paediatric patients with NF1 who have PN	25%	135	Nguyen et al. 2011[6] and Boulanger et al. 2005[7] (mean average taken)
PN which are symptomatic	55%	74	Nguyen et al. 2012[78] (upper end of range taken for a conservative estimate)
Proportion of PN which are inoperable	50%	37	Waggoner et al. 2000[79] Serletis et al. 2007[15] (Mean average taken)
Total eligible patient population	**-**	**37**	Calculated from above

Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

Patients with NF1 in England have a reduction in life expectancy of 8–15 years.[92, 93] This was used to calculated the life expectancies of male and female patients with NF1 PN (Table B2). As outlined in Section 6.1, studies have noted a higher mortality rate for NF1 PN patients than for

the general NF1 population. Therefore, the calculated life expectancy for a patient with NF1 PN is expected to be an overestimate.[76]

Table B2. Life expectancy calculations for NF1 PN patients in England

Life expectancy estimate	Males	Females	Source
Life expectancy from birth in England	79.7 years	83.3 years	Office for National Statistics, 2020[94] (2017–2019 data)
Reduction of life expectancy due to NF1 PN in England	8–15 years	8–15 years	Evans et al. 2011[92]
Calculated life expectancy from birth for a patient with NF1 PN in England	64.7–71.7 years	68.1–75.1 years	Calculated from above

Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.

7 Impact of the disease on quality of life

Summary of Section B7

- **NF1 PN has a substantial impact on the HRQoL of patients**, affecting their physical health, emotional wellbeing, social development and everyday lives[24, 25]
    - In a recent observational study of 140 paediatric patients with NF1 PN, children reported worse scores on eight of ten HRQoL domains, including meaning and purpose, depression, anxiety, psychological stress experiences, peer relationships, and physical function/mobility, when compared with the general population[25]
    - Evidence from the Natural History study demonstrates that PN-associated morbidities can have a considerable negative impact on patients' HRQoL.[19, 25, 26]
    - Greater pain interference with everyday life is associated with increased depression, anxiety, socialisation difficulties and poorer overall HRQoL[19]
- **PN-associated morbidities can also have a negative impact on the psychological health and wellbeing of NF1 PN patients**, due to the uncertainty surrounding the clinical course of NF1 PN,[25] and the impact of the disease on patients' social functioning.
- Disfiguring PNs (e.g. on the face) can lead to anxiety and self-consciousness, concerns around body image, stigma and bullying,[6, 26, 27] culminating in social isolation
- **In the absence of disease-modifying treatment, patients experience PN-associated morbidity and reduced HRQoL throughout their lives, with little hope of improvement**.[11, 17, 19]
    - Adult patients describe the interference of physical PN symptoms in their daily lives, a continued burden of visual disfigurement, and negative impacts on their careers
- **NF1 PN has a clear impact on the daily lives and HRQoL of parents, families and carers**:
    - Parents and carers of paediatric patients with NF1 PN describe providing multiple types of support, such as arranging and managing care through hospital appointments, managing patient symptoms, supporting daily activities, and providing educational, emotional and physical support to their child.[27]
    - Support is required into adulthood: the uncertainty surrounding PN growth and PN-associated morbidities can be a constant source of anxiety for families and carers[14, 27], and carer duties can lead to missed working hours and productivity loss[29]
- Results from Stratum I of the SPRINT Phase II trial demonstrate that **selumetinib treatment leads to significant and durable reductions in PN volume, accompanied by improvements in PN-associated morbidities and patient HRQoL** [18, 34]

- Patients can begin treatment with selumetinib from three years of age. Treatment at a young age prevents or reduces the most rapid stage of PN volume growth. This is anticipated to mitigate the long-term impact of the disease, with a positive impact on HRQoL lasting throughout patients' lives
- It is anticipated that reductions in PN-associated morbidities with selumetinib will positively impact family and carer QoL, by reducing their caregiver burden and improving their emotional wellbeing

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

A *de novo* study was conducted by AstraZeneca (AZ) in order to investigate the impact of NF1 PN on patient and parent/carer HRQoL (see Section 10 for further details). As part of this study, qualitative semi-structured interviews were conducted with adult patients (aged ≥18 years) with NF1 PN, and parents/carers of paediatric patients (aged <18) with NF1 PN, from the UK.[27] Quotations and findings from these interviews (henceforth referred to as the 'AZ qualitative interviews') have been included below.

Paediatric patient HRQoL

NF1 PN has a substantial impact on the HRQoL of patients, affecting their emotional wellbeing, social development and everyday lives. In a recent observational US study, 140 paediatric patients with NF1 PN completed PROMIS and Neuro-QoL. The children reported worse scores on eight of ten HRQoL domains, including meaning and purpose, depression, anxiety, psychological stress experiences, peer relationships, and physical function/mobility, when compared with the general population.[25]

Evidence from the NCI Natural History study demonstrates that PN have a substantial negative impact on HRQoL through the burden of morbidities.[19, 25, 26] Physical functioning impairments such as motor, airway, vision or bowel and bladder morbidities limit patient participation in physical activities with peers.[25, 26] Children with NF1 PN are often unable to participate in educational and social activities due to the impact of PN-associated morbidities, which has a substantial emotional impact on both the child and their family.[70]

Poorer HRQoL in NF1 PN patients is directly correlated with pain interference (the degree to which pain interferes with daily functioning). Wolters et al. identified that greater pain interference was associated with increased socialisation difficulties and poorer overall HRQoL.[19] A further study found that as a result of pain, patients feel a need to be careful during physical exercise, or to limit their participation in physical activity.[70]

Visual disfigurement can have a significant negative impact on patients' wellbeing. Patients express self-consciousness, and concerns around body image and stigma, which can be directly linked to PN-associated disfigurement.[26, 27] Regarding self-consciousness in childhood and adolescence, one UK adult patient explained in the AZ qualitative interviews that:[27]

[redacted]

Disfigurement may make children with NF1 PN more vulnerable to bullying, further exacerbating the emotional and psychological burden of the disease.[95] In the AZ qualitative interviews, [redacted]. This conveys that NF1 PN not only impacts the way patients feel, but how they are treated in society.

The uncertainty surrounding the clinical course of NF1 PN, and the prospect of further disease progression and increasing morbidity, has been identified as a key source of anxiety for patients.[25] The prevalence of anxiety and depression has been demonstrated in a study investigating the impact of NF1 PN on social-emotional functioning and HRQoL, which identified that 10% of patients were using antidepressants.[19] The need for psychological support is indicated through the presence of a Consultant Child Psychiatrist within the multi-disciplinary team managing NF1 PN patients in the specialist centre in Manchester (see Section 8 for further details).[59]

Case studies have further highlighted the impact of the disease on individual patients' psychological health and wellbeing. In a case study of a patient hospitalised due to morbidity from internal PN, it was found that they had been using antidepressants since the age of 17 and had suffered panic attacks since the age of seven. It was reported that these panic attacks were usually triggered by anxiety about the future and progression of the disease. The patient stated that *"this tumour is shredding my nerves day by day, both literally and figuratively"*. By their early twenties, the patient had become bed bound as a result of nerve compression from their PN and was experiencing suicidal ideation. This case study illustrates the severe and long-term impact of NF1 PN on patients' psychological health which continues into adulthood.[14]

Finally, the need for medical treatment and hospitalisation can lead to children's time being taken away from school, preventing them from participating in lessons and building relationships with their peers.[25]

Adult patient HRQoL

Patients with NF1 PN experience unpredictable and uncontrolled growth of PN (see Section 6.1),[11, 18, 19] associated with increases in the number and severity of morbidities over time, correlated with reduced HRQoL.[11] As PN rarely shrink spontaneously, patients continue to face PN-associated morbidities and reduced HRQoL into adulthood, with little hope of improvement.[11, 17, 19]

In the AZ qualitative interviews,
[redacted]

Adult NF1 PN patients also experience a continued burden of disfigurement.
[redacted]

[redacted] One adult patient described:[27]

"I've got the plexiform on my face, so I'm used to certain comments when I'm out, looks, so I tend not to go out as much, or I pick where I'm going."

Finally, adult patients described experiencing negative impacts on their career.[27] In the AZ qualitative interviews, [redacted]

Family and carer QoL

NF1 PN has a clear impact on the daily lives and QoL of families and carers. Most children with NF1 PN require support with their daily activities throughout childhood; this need for support may extend into adulthood. As the condition is heritable, multiple members of the same family may be affected;[1] carers may therefore be caring for more than one family member with NF1, placing a large burden on them. In a cross-sectional study of US NF1 PN carers (n=95), around 50% of carers reported a burden ranging from mild to severe.[29]

In the AZ qualitative interviews, parents and carers of paediatric patients with NF1 PN described providing support in many ways, including managing and monitoring patients' symptoms, supporting with daily activities, and providing educational, emotional and physical support.[27] [redacted]

The burden of caregiving has an emotional impact on parents and carers. The uncertainty surrounding PN growth and PN-associated morbidities can be a constant source of anxiety for families and carers.[14, 27] Parents and carers of paediatric NF1 PN patients express concerns

around the physical, emotional and psychological health of the children they care for, and concerns about not knowing what care is best for their child.[25, 26, 96]

The burden of caregiving for patients with NF1 PN can also impact the daily activities and social lives of carers.[27] [redacted]

Amongst 95 US NF1 PN carers, an average of 17.2% of regular daily activities were hindered by providing care for their child with NF1 PN.[29] Parents may therefore find it challenging to keep normality at home while attending to the needs of their affected children, such as managing medical appoints; unaffected siblings will also be impacted and may find it difficult to understand the situation.

Finally, caring for children with NF1 PN can also have a negative impact on carers' careers. In the AZ qualitative interviews, [redacted] Employed NF1 PN carers in the US (n=95) reported missing an average of 6.9% of their working hours (absenteeism) and an average reduction of 17.3% of on-the-job effectiveness (presenteeism), contributing to an average reduction of 22.3% of work productivity in the past week.[29]

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Impact on patients

Once licensed, selumetinib will be the first pharmacological treatment for NF1 PN available in the UK. Selumetinib is a MEK1/2 inhibitor, targeting the underlying cause of PN growth by selectively inhibiting the RAS/RAF/MEK/ERK signalling cascade to regulate abnormal cell proliferation and induce tumour cell death.[34, 35, 97-99] Further information on the mechanism of action of selumetinib is presented in Section 2.2.

PN growth is associated with increases in the number and severity of morbidities over time.[11, 18, 19] Through inhibition of the RAS/RAF/MEK/ERK signalling cascade, selumetinib prevents PN growth and promotes PN shrinkage, thereby reducing the burden of PN-associated morbidities. Results from Stratum I of the SPRINT Phase II trial (Section 9.6) demonstrate that selumetinib treatment leads to significant and durable reductions in PN volume, accompanied by improvements in PN-associated morbidities and HRQoL.[18, 34]

Selumetinib treatment has been demonstrated to have positive impacts on patients' morbidities and HRQoL; [redacted] of patients treated with selumetinib showed a clinically meaningful improvement in HRQoL, and improvements in PedsQL domain and overall scores were [redacted][34] As shown by the SPRINT Phase II Stratum I data presented in Section 9.6, selumetinib results in meaningful decreases in pain intensity and pain interference with daily functioning, as well as meaningful increases in mobility, physical and airway functioning.[34] Selumetinib is therefore expected to reduce the need for pain medication and improve the daily lives of patients. Improvements in both pain and physical function with selumetinib are also expected to reduce the need to take time away from school for medical treatment.

Reductions in PN growth will reduce the uncertainty surrounding the condition and the likelihood of further morbidities. Selumetinib is therefore expected to reduce anxiety and improve overall emotional wellbeing of the patient.[28] In addition, SPRINT Phase II Stratum I data presented in Section 9.6 demonstrate that reductions in PN volume with selumetinib can reduce disfigurement, thereby reducing patient concerns around body image, further improving the mental health and wellbeing of patients.[18, 34] Reduced disfigurement would also be anticipated to reduce the stigma experienced by patients, and improve patients' ability to interact socially.

Treatment with selumetinib can begin from as early as three years of age and can continue as long as treatment is tolerable and clinical benefit is observed (see Section 2.2.1).[37] Given that the highest PN growth rates have been observed in young children (Section 6.1),[16, 17] it can be expected that starting selumetinib treatment early will be most impactful in stabilising or reducing PN volume, mitigating the burden of disease from an early period of rapid growth. This would prevent PN from reaching large volumes, developing new morbidities and increasing the severity of existing morbidities.

The burden of PN continues into adulthood in the absence of disease-modifying treatment. As the SPRINT Phase II Stratum I data demonstrated that selumetinib treatment leads to durable reductions in PN volume (Section 9.6),[18, 34] the positive impacts of selumetinib treatment are also anticipated to last into adulthood, when PN growth has generally plateaued,[16, 17] and provide a lifelong benefit. The benefits for patients in adulthood may include: increased independence through the ability to perform daily activities of living; improved wellbeing and increased social interactions, due to a decreased burden of disfigurement; and improvements in the workload that adult patients would be able to maintain, due to improvements in the physical symptoms of their PN.

Impact on family and carers

Reductions in PN-associated morbidities as a result of selumetinib treatment can be expected to positively impact family and carer HRQoL.[28] Where parents/carers typically would have substantial anxiety at the prospect of disease worsening (e.g. where a PN suddenly grows, becomes more disfiguring/painful), improvements in patient morbidities and HRQoL with selumetinib would be expected to alleviate these worries and concerns, subsequently improving their wellbeing.[28] In addition, the reduction in time that patients need to take away from school is likely to reduce the negative impact on the daily routines of families and carers. This will result in an improvement in the social lives of carers, as well as their productivity at work.

The positive benefits of selumetinib can be cascading, from the patient themselves to parents/carers and the wider family.

8 Extent and nature of current treatment options

Summary of Section B8

- **Surgery is currently the only treatment that can reduce PN volume to alleviate associated morbidities**. **However, many PN are deemed inoperable** due to the risks associated with surgery, and uncertainty surrounding the outcomes and benefits of surgery for individual patients. In addition, the clinical benefit of partial resection is often unclear, and the risk of PN regrowth high[32]
- **There are currently no available or approved pharmacological treatments to cure, prevent or reduce the volume of inoperable PN**. Without surgery, and in the absence of disease-modifying treatments for NF1 PN, patients must rely solely on symptomatic management, ranging from pain medication to case-specific interventions such as tracheostomy to alleviate severe airway morbidities[11, 19, 33]
- **Selumetinib is the first pharmacological treatment to demonstrate significant reductions in PN volume and PN-associated morbidity**, and has been shown to be tolerable in paediatric patients.[18, 34]
- Selumetinib offers an innovative and much needed treatment, and would represent a step-change in the management of NF1 PN

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

Diagnosis

Whilst there are no NICE guidelines or guidance documents for the diagnosis of NF1 PN, international diagnostic criteria for NF1 were developed by the National Institutes of Health (NIH) at the 1988 NIH Consensus Development Conference.[2, 100] These criteria were reviewed and revised by an international consensus panel of neurofibromatosis experts, including experts from across England and Wales; these updated criteria were published in 2021.[101] These criteria are generally accepted and will be used by clinicians in the UK.

The revised diagnostic criteria, published in 2021, are presented in Table B3.[101] The diagnostic criteria are met if two or more of the criterion are present in an individual who does not have a parent diagnosed with NF1. The diagnostic criteria are met if one or more of the criterion are present in a child of a parent diagnosed with NF1.[101] Of note, part of the rationale for the review of the NIH diagnostic criteria was the clinical availability of *NF1* genetic testing, with a high detection rate; genetic testing is now part of the formal criteria for diagnosis of NF1.[101] Clinical experts have confirmed that NF1 patients usually undergo genetic diagnosis in the UK, and that as NF1 is a heritable condition, family members would also receive genetic testing.[59]

In addition, national guidelines for the diagnosis and treatment of NF1 have been developed in the US and France.[102-104]

Table B3. I-NFDC diagnostic criteria for NF1

Category	NIH NF1 diagnostic criteria
Clinical features	Six or more café au lait macules (>0.5 cm in pre-pubertal individuals or >1.5 cm in post-pubertal individuals)[a]
	Freckling in the axillary or inguinal region[a]
	Two or more neurofibromas of any type (cutaneous and/or plexiform) or one PN
	Optic pathway glioma
	Two or more Lisch nodules (identified on slit lamp examination) or two or more choroidal abnormalities (defined as bright, patchy nodules imaged by OCT/NIR imaging)
	A distinctive osseous lesion (such as sphenoid dysplasia,[b] anterior bowing of the tibia, or pseudarthrosis of a long bone)
Genetic features	A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

Footnotes: [a]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but, as an exception, the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral. [b] Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.
Abbreviations: I-NF-DC: International Consensus Group on Neurofibromatosis Diagnostic Criteria; NF1: type 1 neurofibromatosis; NIH: National Institutes of Health; NIR: near-infrared reflectance; OCT: optical coherence tomography; PN: plexiform neurofibroma.
Source: Legius et al. 2021.[101]

For the diagnosis of NF1 PN, PN must also be identified. Visible PN may be diagnosed when they first appear or be identified following annual routine physical examinations. However, PN are thought not to be visible, except through imaging, in 20% of NF1 patients; this can lead to delays in diagnosis (see Section 8.3).[2] MRI is the standard imaging modality for the diagnosis of PN, especially those which are not visible externally.[11, 30] US guidelines recommend that NF1 patients who experience new neurological symptoms, such as focal limb weakness or sensory changes, should undergo MRI to evaluate whether PN are present.[102, 103]

Clinical management of NF1 PN

There are no NICE guidelines or guidance documents for the treatment and management of NF1 PN. However, information and guidance for patients with NF1 published on the NHS website states that:[105]

- Children with NF1 should have a comprehensive examination once a year, including skin examination for PN
- Adults with NF1 should have regular assessments
- Patients who develop complex problems are referred to one of two specialist treatment centres: Guy's and St Thomas' NHS Foundation Trust (Evelina London Children's Hospital) and Manchester University NHS Foundation Trust (St Mary's, Manchester)

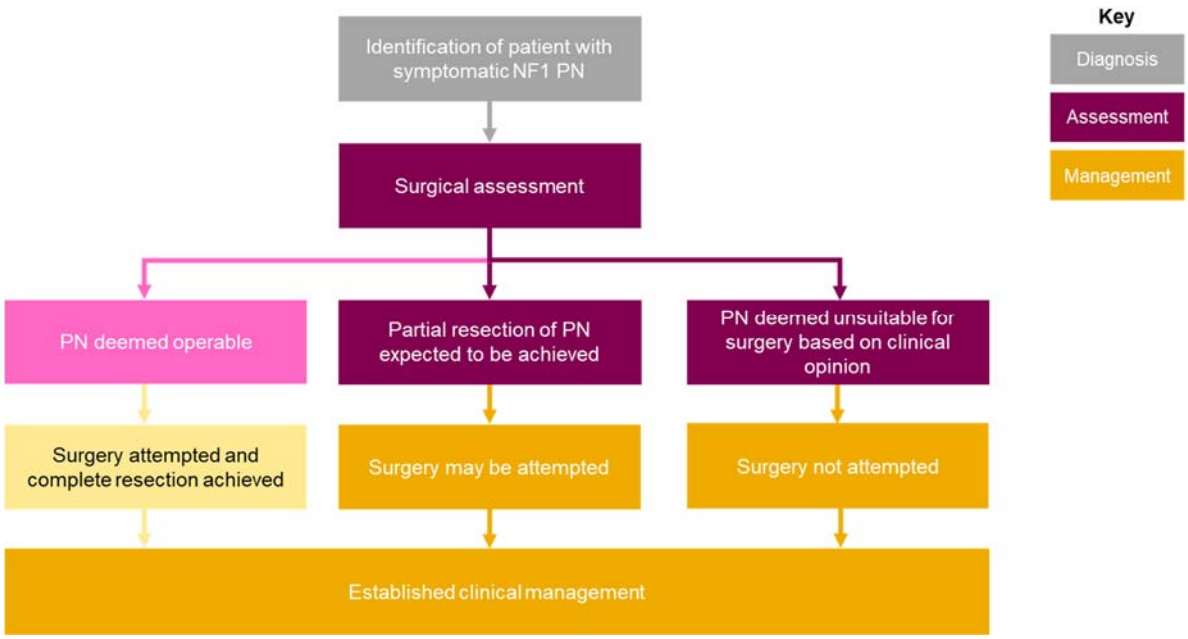
In addition, a 2007 collaboration between members of the UK Neurofibromatosis Association Clinical Advisory Board led to the development of guidelines for the diagnosis and management of NF1.[2] These guidelines refer to the original NIH diagnostic criteria and discuss the clinical manifestations and strategies for the monitoring and management of patients with NF1.[2] The guidelines state that management for NF1 patients should be focussed on age-specific monitoring of disease manifestations and patient education. NF1 patients should be encouraged to seek clinician review of new or unusual symptoms, due to the risk of severe complications such as MPNSTs arising. All paediatric patients with uncomplicated NF1 should be assessed once a year, and adults should also be offered the opportunity to attend a specialist neurofibromatosis clinic for assessment on an annual basis.[2] Education about NF1, its possible complications and inheritance should be provided for patients, particularly those aged 16–25.[2]

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Overview of clinical pathway of care

The current care pathway for patients with NF1 PN, from NF1 diagnosis to treatment of PN, is shown in **Error! Reference source not found.**. In the UK, NF1 patients are referred to either Guy's and St Thomas' NHS Foundation Trust (Evelina London Children's Hospital) or Manchester University NHS Foundation Trust (St Mary's, Manchester) for confirmation of diagnosis. From here, a single multidisciplinary team operates across both centres and discusses all patients.[28] Individual treatment plans are developed for each patient, accounting for individual patient needs and their clinical presentation.[2, 105]

Figure B6. Clinical care pathway for NF1 PN patients



Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.
Source: SPRINT Phase II protocol;[38] Ferner et al. 2007.[2]

Inoperable PN

As discussed in Section 6, the majority of PN are symptomatic, and are associated with morbidities such as pain, disfigurement and difficulties with physical functioning.[9, 11-13] Treatment options for patients with symptomatic NF1 PN are limited, with surgery being the only option for reducing PN volume and associated morbidities. Surgery comes with many risks and limitations, with the overall rate of complications in paediatric patients following PN surgery believed to be around 17–19%.[9, 12] Patients require careful monitoring during surgery. Even when preventative measures are in place, massive haemorrhages, which may be life-threatening, can occur during PN surgeries.[106, 107] One study identified that five of 52 NF1 PN patients undergoing surgery experienced acute surgical complications of bleeding or haematoma.[31] A study of the burden of surgery in the US found that, of the patients who underwent surgery (n=32), 16% reported complications, including post-operative complications (60% of patients with complications) and post-operative symptoms (40% of patients with complications).[88] In addition, it may only be possible to operate on one PN at a time, meaning multiple surgeries may be required if the patient has multiple symptomatic PN.

Many PN are deemed inoperable (see Glossary of terms) due to the risks associated with surgery, and the balance of risk/benefit surrounding the outcomes and benefits of surgery for individual patients. A study of surgery in 52 adult NF1 PN patients found that 10% of patients reported only partial relief of their symptoms and 31% reported no change in symptoms following surgery.[31] Owing to the associated risks (such as bleeding), surgery is not typically considered in UK clinical practice unless PN cause functional or cosmetic issues.[28] In many cases, complete resection is not possible and the goal of surgery is simply to debulk large tumours.[108] PN which are not completely resected (referred to as 'partially resectable', see Glossary of terms) can regrow and continue to cause morbidities, with the estimated rate of recurrence ranging from 29–45% of cases.[32] Additionally, there is some evidence from paediatric patients that even PN that have been completely resected can recur, in up to 20% of cases.[32] As a result of recurrence, approximately 40% of PN may require multiple surgeries.[9, 12, 32]

Symptomatic management and psychological support

Treatment options for symptomatic NF1 PN are particularly limited because PN are considered to be unsuitable for treatment with traditional antineoplastic agents such as radiotherapy and chemotherapy, due to the risk of malignant transformation.[20] Similarly, there are currently no available pharmacological treatments to cure, prevent or reduce the volume of inoperable PN. Although a number of drugs have been evaluated in this population, few have shown clinical benefit, and none have been approved for use in patients with NF1 PN.

Without surgery, and in the absence of disease-modifying treatments for NF1 PN, patients must rely on palliative care and symptomatic management only, such as pain medication, or interventions such as tracheostomy to alleviate severe airway morbidities.[11, 19, 33] Methods of symptomatic management are part the established clinical management for PN-associated morbidities, as described in Table B4.

Between 33–44% of NF1 PN patients receive treatment for the management of pain, including prescriptions for opioid painkillers.[19] However, despite this medication, many patients (in one study, 14/15 adolescent patients) still report pain interference with everyday life.[19] Furthermore, long-term pain medication use is known to have adverse effects, particularly for opioid medications, which are associated with risks of substance abuse, addiction, bone fracture and

cardiovascular events.[109] Patients may also require multiple pain medications, with the number of required medications often increasing as PN grow.[11] Therefore, established clinical management often does not control NF1 PN-associated pain sufficiently.[11]

Mental health support may be provided to patients with NF1 PN. For example, the multi-disciplinary team at the Manchester specialist centre includes a clinical psychiatrist to whom patients may be referred.[28] Pharmacological interventions may also be required to manage patients' mental health, as NF1 PN can result in both anxiety and depression. One study investigating the impact of NF1 PN on social-emotional functioning and HRQoL identified that 10% of patients were using antidepressants,[19] and a case study of a patient in the UK has identified the use of medication for both depression and anxiety in an NF1 PN patient.[14] The impact of NF1 PN on patients' HRQoL and mental health is discussed in Section 7.1.

Table B4. Established clinical management for PN-associated morbidities

PN-associated morbidity	Established clinical management for PN-associated morbidities
Pain	• Multiple pain medications including scheduled, neuropathic and opioid pain medications[11] • Physical therapy may be beneficial[103]
Motor	• Due to significant muscle weakness and disability, the patient may require use of a wheelchair or assistive devices[14] • Physical therapy may be beneficial[103]
Airway	• Airway obstruction requires patients to undergo tracheostomies[86] • Airway PN can cause morbidities such as sleep apnoea which may be treated with continuous positive airway pressure[33, 87]
Bladder and bowel	Management of PN-associated bladder morbidities follows the general management for bladder problems:[110, 111] • Incontinence products such as absorbent products, handheld urinals • Medicines such as antimuscarinics or diuretics • Interventional bladder surgery may be considered if other treatments are unsuccessful Management of PN-associated bowel morbidities follows the general management for bowel problems:[112] • Continence products such as foam plugs or pads • Medicines such as loperamide or laxatives • Interventional bowel surgery may be considered if other treatments are unsuccessful
Vision	• In some cases, visual loss can be treated or corrected for non-surgically, for example in cases of eye misalignment (strabismus) caused by PN restricting eye movement[13] • The value of surgery for orbital and periorbital PN is unclear, as these PN often recur and there is a risk of facial nerve damage and unwanted alterations in appearance[13]

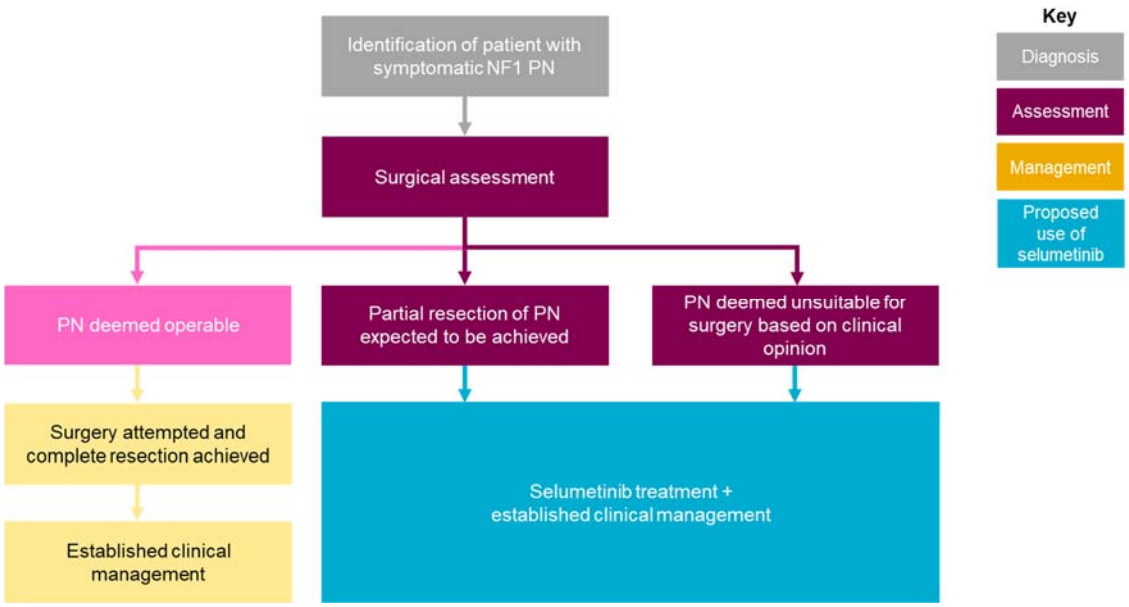
Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.

Clinical care pathway with selumetinib

The proposed treatment pathway for patients with NF1 PN following the introduction of selumetinib is shown in Figure B7. For NF1 patients with symptomatic PN expected to be partially resected or deemed unsuitable for surgery, selumetinib treatment would offer a

treatment option beyond established clinical management only. Patients may continue to require symptomatic management, post-operatively or concomitantly with selumetinib treatment.[31, 34]

Figure B7. Pathway for the treatment of NF1-related PN with selumetinib



Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.
Source: SPRINT Phase II protocol;[38] Ferner et al. 2007.[2]

It has been reported that PN may recur after complete resection in up to 20% of cases.[32] It is assumed that PN which recur after complete resection would be assessed for morbidities and suitability for surgery in the same manner as a newly identified PN. The recurrent PN would then be treated based on the surgical assessment of operability.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Delays in diagnosis

NF1 is a rare disease, with a prevalence of 1 in 4,560 in England (Section 6.2);[113] additionally, approximately 25% of NF1 patients develop PN,[6, 7] resulting in a small paediatric NF1 PN patient population. Few general practitioners (GPs) to whom NF1 PN patients will initially present will have had first-hand experience of the condition. Despite clear guidelines for the diagnosis of NF1 PN (see Section 8.2), low awareness of NF1 PN amongst non-specialist clinicians may lead to delays in diagnosis and/or misdiagnosis. Such delays in diagnosis, and subsequent referrals to specialist centres, result in delays to patients accessing appropriate care, such as established clinical management, surgery and, in the future, disease-modifying treatment.

As described in Section 6.1, young children experience the most rapid rates of PN growth. Without disease-modifying treatment, this leads to rapidly increasing PN volume and the development of PN-associated morbidities; PN-associated morbidities do not resolve

spontaneously.[11] Improvements in time to diagnosis and access to future disease-modifying treatment by young children would therefore contribute to improved outcomes for patients.

Surgical operability in children

Surgery is currently the only management strategy that can reduce PN volume to alleviate associated morbidities. However, as described above there are challenges surrounding the use of surgery for NF1 PN patients. In many patients only partial resection of PN can be achieved,[32, 114] the clinical benefit of partial resection may be unclear, and the risk of PN regrowth is high.[9] Additional evidence from patients suggests that surgeries may become more complex as patients grow into adulthood and PN become larger and more invasive.[75]

Given the variability of the outcome of surgery, alongside the risks and potential negative side-effects of it,[9, 12, 31, 100, 115] there may be variation into what constitutes the most appropriate symptomatic management of NF1 PN.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

The introduction of selumetinib will enable patients to have access to the first disease-modifying treatment for NF1 PN, leading to better care and improved outcomes for patients. It would also provide a much-needed pharmacological option for patients with symptomatic PN that are inoperable.

It is envisaged that selumetinib treatment would be delivered by the two specialist UK centres: Guy's and St Thomas' NHS Foundation Trust (Evelina London Children's Hospital) and Manchester University NHS Foundation Trust (St Mary's, Manchester).

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Selumetinib offers an innovative and much needed disease-modifying treatment, which, if it becomes routinely available, would represent a step-change in the management of NF1 PN disease. Selumetinib treatment is the first pharmacological treatment to demonstrate significant, durable reductions in PN volume and improvements in PN-associated morbidity for NF1 patients with symptomatic, inoperable PN.[18, 34]

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Treatment with selumetinib would most likely be managed via the current MDT for NF1 in the UK (run from the Evelina London Children's Hospital and St Mary's Manchester), where a route for MEK inhibitor treatment (clinical trials) already exists.[2, 28, 105] As a safe, oral treatment, it is anticipated that no major changes to the way current services are delivered would be required for the introduction of selumetinib.[28]

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Currently, in the absence of an active treatment available for NF1 PN, patients are monitored by annual routine MRI scans and/or physical examinations. No additional tests or investigations would be required for identifying or selecting patients for treatment with selumetinib. Patients receiving selumetinib are likely to require monitoring for the duration of treatment, which may include up to two additional MRI scans per year.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure beyond those already in use are needed.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Selumetinib is likely to reduce the need for medical facilities and technologies used to treat PN-associated morbidities including airway-related interventions such as tracheostomy and, as a result of improved HRQoL, reduced need for psychological support services.[34, 86]

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Methodology of Relevant Studies (Section 9.4)

An SLR was conducted to identify all published and unpublished studies of the treatment of patients with NF1 with inoperable PN; eight published studies (Section 9.3). The most relevant study to the decision problem captured in the SLR was Stratum I of the SPRINT Phase II study, which represents the primary source of evidence for selumetinib in this indication (Section 9.4):[18, 38]

- SPRINT is a Phase I/II, multicentre, open-label clinical trial examining the efficacy, safety and tolerability of selumetinib for the treatment of PN in paediatric NF1 patients.[18, 38] Stratum I of the trial provides evidence for the target population for this submission, investigating selumetinib in paediatric patients, aged 2−18 years, with NF1 and symptomatic, inoperable PN[38, 40]
- The primary objective of Stratum I was to evaluate the confirmed partial and complete response rate of selumetinib using volumetric MRI analysis[38, 40]
- In order to determine the comparative effectiveness of selumetinib vs established clinical management, non-randomised comparisons vs external control data were explored:
    - A naïve comparison between SPRINT Phase II Stratum I and an age-matched cohort of the NCI Natural History study[18]
    - A naïve comparison of PFS between SPRINT Phase II Stratum I and patients with progressive PN from the placebo arm of tipifarnib Study 01-C-02220222[41]
- These external comparisons were planned as part of the protocol for SPRINT Phase II Stratum I

Results of SPRINT Phase II Stratum I (Sections 9.6 and 9.7)

- The trial recruited 50 patients with a median age of [redacted] years. The patients exhibited a range of PN sizes, locations and morbidities; median target PN volume was [redacted] and PN were associated with a median of [redacted] PN-related morbidities (Section 9.4.3)[34]
- **Selumetinib treatment results in durable reductions and stabilisations in tumour volume in children with symptomatic, inoperable NF1 PN**.
    - The median change in PN volume in patients treated with selumetinib in SPRINT Phase II Stratum I was a 23% decrease from baseline, compared to a 77% increase from baseline observed in the age-matched Natural History cohort.[18] Tumour size reduction of any extent is rare in this disease setting, demonstrating the step-change in clinical efficacy provided by selumetinib
- **Children receiving selumetinib in the SPRINT trial had a higher probability of PFS over three years of follow-up compared with the Natural History study age-matched**

cohort (84% vs 15%), demonstrating the stabilisation of patient's PN in the SPRINT trial vs the Natural History trial.[18]

  - Children receiving selumetinib in the SPRINT trial also had a higher probability of PFS at two years compared to patients receiving placebo in the tipifarnib study [redacted][34]

  - Four different methods of propensity score matching were performed to improve the comparability of the SPRINT and Natural History study populations (Section 9.8.1). The results were robust to the choice of method and consistently support the benefit of selumetinib in reducing the risk of progression

- **Results from functional assessments of PN-associated morbidities demonstrate that selumetinib treatment led to improvements in functional outcomes**, including level of pain (NRS-11, PII), strength (manual muscle test), mobility (PROMIS), and airway functioning ($FEV_1/FEV_{0.75}$, R_{20})[34]

- **The clinical improvements seen with selumetinib treatment have a positive impact on patients' everyday lives, through improved HRQoL**.

  - Based on self-reported PedsQL total scores, [redacted] patients showed a clinically meaningful improvement in HRQoL. Based on parent-reported PedsQL total scores, [redacted] patients showed an improvement in HRQoL. [redacted][34]

- **Selumetinib has been shown to be tolerable in paediatric patients.** Although the majority of patients in the trial reported adverse events (AEs), they were mostly mild or moderate in severity[18, 34, 42]

  - AEs could generally be managed using dose interruptions or symptomatic/supportive care, rather than through treatment discontinuation, and subsequently resolved. No irreversible or cumulative toxic effects were noted[18, 42]

- **Overall, results from SPRINT Phase II Stratum I show that selumetinib treatment is well-tolerated and effective in reducing and stabilising tumour volume, increasing PFS and improving HRQoL for paediatric patients with symptomatic, inoperable NF1 PN**[18, 34, 42]

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A single SLR was conducted to identify all published studies concerning the treatment of patients with NF1 and inoperable PN. The eligibility criteria for this SLR are provided in Table C1 (Section 9.2.1) and a record of included and excluded studies is given in the Appendix (Section 17.1.8).

Full details of the SLR methodology taken are provided in the Appendix (Section 17.1); in summary, the strategies taken were:

- A search of the following electronic databases:
    - Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (searched via the Ovid SP platform, 1946 to 25 January 2021)
    - Embase (searched via the Ovid SP platform, 1974 to 25 January 2021)
    - The Cochrane Database of Systematic Reviews (CDSR) and Central Register of Controlled Trials (CENTRAL), simultaneously via The Cochrane Library Wiley online platform, Issue 1 of 12, January 2021
    - The Database of Abstracts of Reviews of Effects (DARE), via the University of York Centre for Reviews and Dissemination (CRD) platform, Issue 2 of 4, April 2015
- A manual search of proceedings from the following conferences:
    - International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – International and European meetings, 2018, 2019 and 2020
    - Joint Global Neurofibromatosis Conference (JGNC) – 2018 (this event combined the Children's Tumor Foundation NF Conference and European Neurofibromatosis Meetings in that year)
    - Children's Tumor Foundation NF Conference – 2019 and 2020
    - European Society for Medical Oncology (ESMO) – 2018, 2019 and 2020
    - American Society of Clinical Oncology (ASCO) – 2018, 2019 and 2020
    - International Symposium on Pediatric Neuro-Oncology (ISPNO) – 2018 and 2020
    - American Society of Pediatric Hematology/Oncology (ASPHO) – 2018, 2019 and 2020
- Manual searches of the bibliographies of all relevant SLRs and (network) meta-analyses ([N]MAs) identified during the course of the review
- Manual searches of materials provided by AZ, including:
    - A targeted literature review (TLR) conducted in 2019 on NF1 PN clinical studies
    - A TLR conducted in 2020 to capture HRQoL instruments in NF1

Full details of each of these search strategies are provided in the Appendix (Section 17.1.4).

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

An additional search of ClinicalTrials.gov, run by the United States National Library of Medicine at the National Institutes of Health, was performed to ensure that any relevant, unpublished data was identified. Relevant studies were cross-checked against the results from the database searches (Section 9.1.1) to avoid duplication of included studies.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

A prior SLR by Copley-Merriman et al., published in 2021, was conducted to identify studies reporting on the natural history, disease burden, and treatment patterns among patients diagnosed with NF1 and PN. This natural history SLR included 39 publications of studies exploring these topic areas, including five exploring PN growth. In light of the comprehensive overview of relevant observational data provided by the Copley-Merriman SLR, the clinical literature review informing this evidence submission was designed to identify controlled studies, investigating selumetinib against the relevant comparator of established clinical management, as per the decision problem.[116]

The inclusion and exclusion criteria for the SLR were defined before conducted searches and are given in Table C1 below.

Table C1. Selection criteria used for published studies

	Inclusion criteria	Exclusion Criteria	Justification
Population	• Paediatric (aged ≥3 and ≤18 years) and/or adult (aged >18 years) patients with inoperable NF1 PN • Patients were considered inoperable if this was stated in the publication, the publication stated no other treatment options (aside from the administered intervention) were available or patients could only undergo partial resection of PN	• Paediatric and/or adult patients without inoperable NF1 PN • Paediatric and/or adult patients with NF1 but no PN • Paediatric and/or adult patients with PN that can be completely resected	• This includes the patient population relevant to the NICE decision problem for this submission • Adult patients considered in addition to paediatric patients to broaden the scope of the clinical review, due to the anticipated narrow body of evidence available in NF1 PN
Interventions	• Selumetinib	• Any other intervention or emerging therapies, including symptomatic, supportive treatments (e.g. binimetinib, trametinib, carbozantinib, mirdametinib, pain management, tracheostomy) • Interventions not considered to be 'emerging therapies' for NF1 PN (tipifarnib, sirolimus, Imatinib, PEG-interferon Alfa-2b, pirfenidone everolimus)	• Aligned to the NICE decision problem
Comparator	• Any (including established clinical management) or none	N/A	• Aligned to the NICE decision problem; no limitation was applied
Outcomes	Efficacy outcomes, including: • Objective response rate • Complete response rate • Partial response rate • Stable disease • Progression free survival • Time to progression	• Studies not presenting relevant outcomes (See Inclusion criteria)	• These outcomes encompass the clinical outcomes specified as relevant in the NICE decision problem for this submission

	• PN volume change • Growth rate of PN • Effect on physical functioning • Effect on pain Safety outcomes, including but not limited to: • AEs (including treatment-related AEs and serious AEs) • Deaths • Discontinuation due to AEs • Discontinuation due to treatment-related AEs HRQoL		
Study design	• RCTs • Interventional non-RCTs, such as controlled (but not randomised) clinical trials and single-arm clinical trials • Observational studies	• Narrative reviews • Economic evaluations	• A broad eligibility was included for study design, with any study design likely to report novel data included in this SLR
	SLRs or (N)MAs of relevant study designs were included at the title/abstract screening stage for the purpose of identifying any additional studies not identified in the database searches, but were ultimately excluded at the full-text review stage		
Publication type	• Peer-reviewed journal articles • Congress abstracts published in or since 2018 • Letters (if they report primary research)	• Non peer-reviewed journal articles (e.g. editorials, commentaries, opinion pieces) • Book chapters • Clinical guidelines • Congress abstracts published before 1st January 2018	
Language restrictions	• Publications with at least an abstract in the English language	• Publications without an abstract in the English language	• An English language limitation was applied to the SLR as the review team did not have the linguistic capacity to review non-English

			language articles.
Other considerations	• Human subjects • Any geographic location	• Studies in animals • In vitro studies in cells, cell lines and/or tissue samples	• Studies on non-human subjects were excluded from the review as these were considered not relevant to the decision problem

Abbreviations: AE: adverse event; HRQoL: health-related quality of life; NF1: type 1 neurofibromatosis; N/A: not applicable; NICE: The National Institute for Health and Care Excellence; (N)MA: (network) meta-analysis; PN: plexiform neurofibromas; RCT: randomised controlled trial; SLR: systematic literature review.

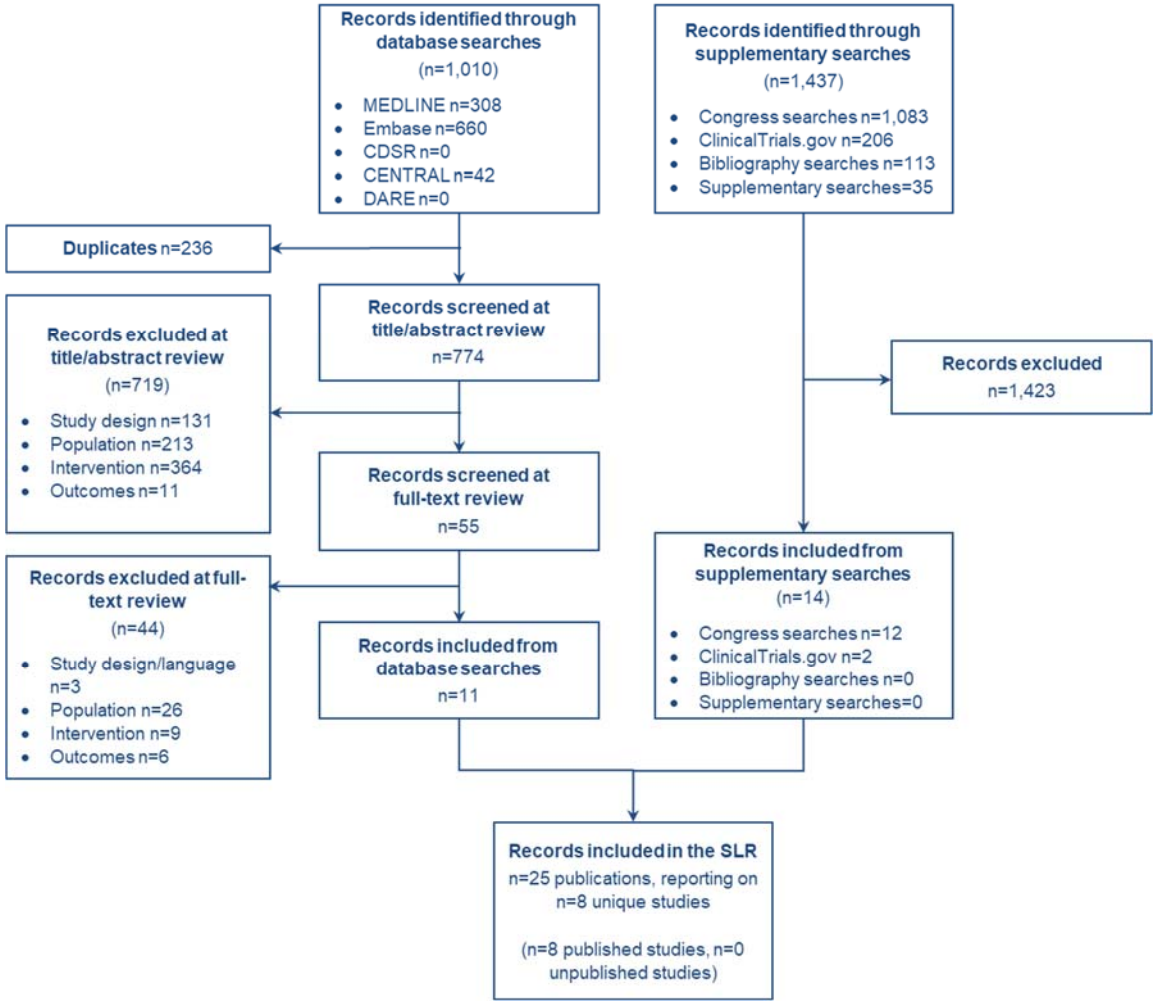
9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the SLR is presented in Figure C.

In the SLR, 1,010 records were retrieved from the electronic database searches, of which 236 were duplicates, meaning 774 novel records were screened at the title/abstract review stage. Of these records, 55 full publications were subsequently screened at full-text review. Following a detailed evaluation of the full texts of these articles, 11 records were identified that met the review inclusion criteria. Figure C lists all the published and unpublished studies included in the SLR.

Supplementary searching identified an additional 14 records that met the inclusion criteria, meaning that a total of 25 publications reporting on eight unique studies (eight published and zero unpublished) were identified reporting the treatment of paediatric patients with NF1 and inoperable PN.

Figure C1. PRISMA diagram for the clinical SLR



Abbreviations: CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; SLR: systematic literature review.

Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Unpublished studies were screened using the same eligibility criteria as for published studies. For full details of the eligibility criteria, please refer to Table C1 in Section 9.2.1.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

206 records were identified through searching ClinicalTrials.gov. No unique, unpublished studies were identified through these records.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Details of the eight published studies meeting the pre-defined inclusion criteria of this review were collected and are reported in Table C3.

Table C3. List of relevant published studies

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)	Supplementary reference(s)
Baldo 2020[117]	Interventional prospective case-series	Baldo 2020	Paediatric patients with NF1 and inoperable PN	Selumetinib	N/A	AEs, tumour response to selumetinib	N/A
Coyne 2019[118]	Phase II, on-interventional	NCT02407405	Adult (≥18 years) patients with NF1,	Selumetinib	N/A	Change in PN volume, partial RR, complete RR, safety,	ClinicalTrials.gov (NCT02407405)[119] Coyne 2020a[120]

	study (single-arm trial)		inoperable PN and ≥1 PN-related morbidity			pharmacodynamics, pain	Coyne 2020b[121] Martin 2019[122] Jackson 2020[a123] Jackson 2018a[a124] Jackson 2018b[a125]
Dombi 2016[39]	Interventional, open-label study	NCT01362803 SPRINT: Phase I	Children with NF1 and inoperable PN	Selumetinib	N/A	PR, time to best response, safety	ClinicalTrials.gov (NCT01362803)[b67], Dombi 2020[c126]
Espirito Santo 2020[127]	Case-series	Espirito Santo 2020	Genetically confirmed NF1 patients (aged 3–19) with inoperable PN associated with significant or potentially significant morbidity	Selumetinib	N/A	Clinical improvement, PN size, clinical/radiological progression, safety	N/A
Glassberg 2020a[128]	Interventional study	SPRINT: Phase II, stratum II	Children and young adults, aged 2–18 years, with NF1 and inoperable PN, without clinically significant baseline PN-related morbidity	Selumetinib	N/A	Response, functional status, safety	ClinicalTrials.gov (NCT01362803)[b67] Dombi 2020[c126] Glassberg 2020b[68] Pichard 2018[d129]

Gross 2020[18]	Interventional, open-label study	NCT01362803 SPRINT: Phase II, stratum I	Patients with NF1 with symptomatic, inoperable PN (aged 2–18 years)	Selumetinib	N/A	ORR, BOR, PR, PFS, functional outcomes, HRQoL, GIC, AEs	AstraZeneca Data on File (SRINT CSR)[34] AstraZeneca Data on File (SRINT Safety update)[58] AstraZeneca Data on File (SRINT SAP)[38] ClinicalTrials.gov (NCT01362803)[b67] Dombi 2020[c126] Gross 2018a[11] Gross 2018b[130] Gross 2018c[131] Gross 2019[132] Hampton 2018[133] Pichard 2018[d129] Wolters 2018[134] Jackson 2020[a123] Jackson 2018a[a124] Jackson 2018b[a125]
Kudek 2019[135]	Interventional, case-report	Kudek 2019	Paediatric NF1 patients with inoperable PN	Selumetinib or trametinib	N/A	Disease progression, AEs	N/A
Passos 2020[136]	Interventional case-study	Passos 2020	14-year-old boy with NF1 and PN, undergone partial resection	Selumetinib	N/A	Lansky Performance Scale, toxicities	N/A

Footnotes: [a]Studies are pooled analyses reporting data on both SPRINT Phase II, stratum 1 and NCT02407405, [b]Study is the ClinicalTrials.gov record associated with SPRINT (Phase I, Phase II Stratum 1, and Phase II Stratum 2), [c]Study is a pooled analysis reporting data on SPRINT trials (Phase I, Phase II Stratum 1, and Phase II Stratum 2), [d]Study is a pooled analysis reporting data on SPRINT Phase II trials (Phase II Stratum 1, and Phase II Stratum 2).
Abbreviations: AE: adverse event; BOR: best objective response; GIC; global impression of change; HRQoL: health-related quality of life; N/A: not applicable; NF1: type 1 neurofibromatosis; PFS: progression free survival; PN: plexiform neurofibroma; PR: partial response: RR: response rate; ORR: objective response rate.

List of relevant unpublished studies

Table C4. List of relevant unpublished studies

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)
No relevant unpublished studies were identified in the clinical SLR.						

9.3.2 State the rationale behind excluding any of the published studies listed in table C3.

None of the published studies which met the inclusion criteria were excluded. Unpublished studies (Table C4) for which no results have been reported were excluded from this review on the basis of insufficient data.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies. A separate table should be completed for each study.

Of the observational and interventional studies captured in the SLR, the SPRINT Phase II Stratum I was considered of greatest relevance to the decision problem, investigating selumetinib for the treatment of paediatric patients with NF1 and symptomatic, inoperable PN. Evidence from this clinical trial supported the marketing authorisation for selumetinib in this indication. Full details of this study are provided below, with the critical appraisal of this study reported in Section 9.5.

The data from SPRINT Phase I trial is in alignment with the data from the SPRINT Phase II Stratum I. In addition, three studies of selumetinib in NF1 patients with inoperable PN in real world settings were identified through the SLR, with results that also support the conclusions from the SPRINT Phase II Stratum I. Details of these studies can be found in the Appendix (Section 17.2), alongside details of other, remaining published studies that were included and captured in the clinical SLR, but considered not relevant to the decision problem. For each study, details of methodology, baseline characteristics, outcomes and adverse events were extracted, and a critical appraisal conducted.

As is common for rare disease indications, studies for selumetinib in the relevant patient population are limited to single arm studies, due to the ethical and practical reasons preventing a randomised, controlled trial (RCT) from being performed. Therefore, in order to determine the comparative effectiveness of selumetinib vs relevant comparators, several pre-planned, non-randomised comparisons vs external controls were explored:[34]

- A naïve comparison between SPRINT Phase II Stratum I and an age-matched cohort from the NCI Natural History study.[18] The NCI Natural History study is a robust, longitudinal study of patients with NF1 PN and provides a comprehensive description of the disease course in a

relatively large patient cohort,[18] therefore making it an appropriate comparator for SPRINT Phase II Stratum I. Additionally, three of the five publications reporting on PN growth identified by the Copley-Merriman SLR reported on this study,[116] emphasising it's pivotal role in informing our current understanding of the natural history of NF1 PN. This external comparison was planned as part of the protocol for SPRINT Phase II Stratum I

- A naïve comparison of PFS between SPRINT Phase II Stratum I and patients with progressive PN from the placebo arm of tipifarnib Study 01-C-0222.[41] The placebo arm of tipifarnib Study 01-C-0222 was designed in such a way that it could be used as an external control for other trials in this indication[41] and has been used as a historic control for other clinical trials, making it highly suitable for use as a comparator for SPRINT Phase II Stratum I data. This external comparison was planned as part of the protocol for SPRINT Phase II Stratum I

Whilst these studies were not captured within the clinical SLR (as the selection criteria required studies to investigate selumetinib as an intervention), due to the importance of the control data from these studies, the study design and methodology of these two studies has been reported below.

SPRINT Phase II Stratum I

The SPRINT Phase I/II study was conducted by the NCI and supported by AZ via a cooperative research and development agreement (CRADA).

As described in Section 4, the SPRINT Phase II trial was designed to evaluate the response rate to, and clinical benefit of, selumetinib treatment. The SPRINT Phase II trial is a single arm study. At the time the trial was designed, it was considered unethical to include a placebo arm in the trial, given that:

- Paediatric NF1 patients with symptomatic, inoperable PN have a significant unmet need (see Sections 6.1 and 7.1) and no effective, disease-modifying medical treatment;

- Paediatric patients enrolled on the SPRINT Phase II trial had substantial PN-related morbidity at study entry;[18] and

- Phase I of the SPRINT trial had demonstrated promising efficacy for selumetinib in this population (ORR 71%)[39]

SPRINT Phase II included two strata: Stratum I included paediatric NF1 patients aged 2−18 with symptomatic, inoperable PN, and is ongoing. The SPRINT Phase II Stratum I population is closely aligned with the decision problem. Although paediatric patients aged 2−18 years were included in the trial, the licence for selumetinib is anticipated to cover patients aged 3−18 years, due to insufficient data from SPRINT in patients aged two years.

To provide context for the SPRINT Phase II trial and enable assessment of the clinical efficacy of selumetinib versus established clinical management, clinical efficacy data were compared to external control data from an age-matched cohort of children with symptomatic inoperable NF1 PN from the NCI natural history study; this external comparison was pre-planned as part of the protocol for SPRINT Phase II Stratum I.

The design and methodology of SPRINT Phase II Stratum I are summarised in Table C5.

Table C5. Summary of methodology of SPRINT Phase II Stratum I

Study name	SPRINT Phase II (NCT01362803)
Objective	To evaluate the confirmed partial and complete response rate to selumetinib in paediatric patients with NF1 with inoperable PN
Location	US (four study centres)
Design	Interventional study (open-label, Phase II)
Duration of study	Trial is ongoing
Patient population	Stratum I: Paediatric patients aged 2–18 years with symptomatic, inoperable PN associated with NF1
Sample size	50
Key inclusion criteria[a]	• Aged 2–18 years • BSA ≥0.55 m^2, if able to swallow whole capsules Diagnosis of NF1: • Positive genetic testing for NF1, or • At least one of the NIH consensus diagnostic criteria additional to PN Inoperable, symptomatic PN: • PN were required to be measurable, defined as a lesion of at least 3 cm, measured in one direction • A PN was defined as inoperable if it could not be surgically completely removed without risk of substantial morbidity due to encasement or close proximity to vital structures, invasiveness or high vascularity o Patients who had previously undergone surgery for a PN were eligible provided the PN was not completely resected and was still measurable • A PN was defined as symptomatic if it caused significant morbidity including (but not limited to) deformity or disfigurement, limb hypertrophy or loss of function, pain, airway or great vessel compromisation, or nerve compression in the regions of the brachial or lumbar plexus
Key exclusion criteria[a]	• Patients for whom the need for surgical intervention of the target PN was anticipated within the first eight cycles of treatment • Use of any investigational agent within the previous 30 days • Ongoing radiation therapy, chemotherapy or hormonal therapy directed at the tumour, immunotherapy or biologic therapy • Inability to undergo MRI or contraindication for MRI • Prior treatment with selumetinib or another MEK1/2-specific inhibitor • Evidence of an optic glioma, malignant glioma, MPNST or other cancer requiring treatment with chemotherapy or

	radiation therapy
Intervention(s) and comparator(s)	**Intervention:** Selumetinib 25 mg/m^2 BSA BID (n=50) **Comparator:** N/A (single arm trial)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Long-term safety follow-up was planned for a duration of seven years from the initiation of treatment, or five years after completion of selumetinib treatment, whichever takes longer. Follow-ups include an annual health check and safety evaluations. Median duration of follow-up as of the most recent DCO (29th March 2019) is three years, based on a median number of 36 treatment cycles (each one month long). One patient was lost to follow-up.
Statistical tests	The sample size for the primary objective was based on a target response rate of >15%. With a total of 50 evaluable, symptomatic patients, an exact binomial test with a nominal one-sided 2.5% significance level will have 90% power to detect the difference between a null hypothesis response rate of 15% and an alternative hypothesis response rate of 36%. No formal hypothesis testing was performed. Descriptive statistics include the number of non-missing patients (n), mean, standard deviation, median, minimum and maximum values for continuous variables, while numbers and percentages of patients are presented for categorical variables. The FAS included all patients who received at least one dose of selumetinib. The FAS was the same as the SAS and the ITT population.
Primary outcomes (including scoring methods and timings of assessments)	• ORR to selumetinib, defined as the rate of confirmed PR and CR (PR defined as PN decrease ≥20% compared to baseline; CR defined as the disappearance of the target PN) using centrally read volumetric MRI A target PN was identified for each patient. The target PN was defined as the clinically relevant PN and was required to be amenable to volumetric MRI assessment. PN volumetric evaluation was scheduled every four cycles for the first 25 cycles, with the first evaluation taking place prior to Cycle 5. After Cycle 25, evaluations were scheduled every six cycles, and at the end of therapy. For long-term follow-up, evaluations were to occur at six-monthly intervals for two years, then every two years or as clinically indicated.
Secondary outcomes (including scoring methods and timings of assessments)	**Tumour Volumetric Responses:** • BOR to selumetinib (see Section 9.6) • Duration of response to selumetinib (see Section 9.6) • Effect of selumetinib on PN growth rate (see Section 9.6) • TTP and PFS in progressive PN (≥20% increase in PN volume within 12–15 months prior to enrolment; see Section 9.6)

	Error! Reference source not found.PN volumetric evaluation was scheduled every four cycles for the first 25 cycles, with the first evaluation taking place prior to Cycle 5. After Cycle 25, evaluations were scheduled every six cycles, and at the end of therapy. For long-term follow-up, evaluations were to occur at six-monthly intervals for two years, then every two years or as clinically indicated. The most clinically relevant PN was selected at baseline by the treating physician as the 'target lesion' and was used to determine treatment response. Assessment of PN response and progression in the trial was conducted using volumetric analysis MRI, performed centrally by the NCI (non-blinded). **Clinical Outcome Measures:** At baseline, all patients were assigned to one or more categories of PN-related morbidity based on the location of their target PN and clinical presentation. This assignment determined the patient- and observer-reported outcomes and the functional evaluations to be completed. HRQoL and pain evaluations were assessed prior to Cycles 3, 5, 9 and 13, then after every 12 cycles (prior to cycles 25, 37, etc). These assessments were collected irrespective of patients' baseline PN-associated morbidities. Functional evaluations were assessed prior to Cycles 5, 9 and 13, then after ever 12 cycles (prior to Cycles 25, 37, etc). These assessments were collected only from patients with those morbidities at baseline. • **HRQoL**: PedsQL total score and the four domain scores: o Physical functioning o Emotional functioning o Social functioning o School functioning • **Pain**: NRS-11, PII, Pain Medication Survey • **Motor function:** PROMIS (mobility and upper extremity), strength, range of motion, grooved pegboard test, grip strength and key pinch, leg length evaluation • **Airway function:** AHI sleep study, PFTs • Bowel/bladder function: DVQ • **Visual function**: Visual acuity, exophthalmometry • **Disfigurement:** Captured via photography • **Physical functioning:** 6MWT (only in patients with lower extremity PN, cord compression or airway PN)

	The primary analysis of the clinical outcome measures was based on descriptive statistics and MMRM analyses summarising the changes over time. MMRM analyses were used to allow for correlation between observations within a subject. Supportive analyses using CMTs were conducted to help with interpretation of clinical benefit. Thresholds for meaningful change were estimated using both distribution (one-half standard deviation) and anchor-based (with the GIC as the anchor) approaches. Whenever available, data from published literature were used to define the CMT. The CMT definitions were as follows: • Improvement: a change from baseline ≥ CMT points • Deterioration: a change from baseline ≤ −CMT points • No change: a change from baseline between (−CMT to CMT) The assessments used for the clinical outcome measures, the assessment timepoints and CMT criteria, are summarised in Appendix 17.7. **Global Impression of Change:** A GIC scale was used to assess change in tumour pain, overall pain and tumour-related morbidities compared to baseline. GIC was assessed at pre-Cycles 3, 5, 9 and 13, then every 12 cycles. **Safety Measures:** • Detailed clinical evaluation • Laboratory studies Evaluations were assessed prior to Cycles 2-5, then every other cycle (prior to Cycles 7, 9, 11 and 13), then every four cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycle 31, 37, 43, etc). • ECG/ECHO or cardiac MRI ECG was assessed as clinically indicated. ECHO was assessed prior to Cycles 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to Cycles 31, 37, 43, etc). • Ophthalmologic exams Ophthalmological evaluations were assessed prior to Cycles 5 and 13, then yearly or more often as clinically indicated. • Symptom checklist • Patient diary • AEs These safety evaluations were assessed prior to Cycles 3, 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to cycles 31, 37, 43, etc). **Other Secondary Outcomes:**

	• Bone mineral density in patients with impaired bone mineral density at the time of enrolment[b] • Day one and steady state pharmacokinetics of selumetinib[c] • Changes in the size of the optic pathway tumour or other glioma[d] • Changes in ERK phosphorylation in PBMCs[e]

Footnotes: [a]For full details of the inclusion and exclusion criteria please see AstraZeneca Data on File (SPRINT protocol, SAP).[40] [b]Data on bone mineral density have not been presented within this evidence submission, as the results are not relevant for the scope of this appraisal. [c]Pharmacokinetic analyses are included in the SPRINT CSR, but have not been presented within this evidence submission as these results are not relevant for the scope of this appraisal.[34] [d]This objective was of an exploratory nature for research purposes, and data were not collected in the clinical database.[40] [e]There was insufficient viable data for this objective to be included in the SPRINT CSR.[34]
Abbreviations: 6MWT: six-minute walk test; AEs: adverse events; AHI: apnoea hypopnoea index; BOR: best objective response; BID: twice daily; BSA: body surface area; CI: confidence interval; CMT: clinically meaningful threshold; CR: complete response; DCO: data cut-off; DoR: duration of response; DVQ: dysfunctional voiding questionnaire; ECG: electrocardiogram; ECHO: echocardiogram; FAS: full analysis set; GIC: global impression of change; ICR: independent central review; ITT: intention-to-treat; KM: Kaplan-Meier; MMRM: mixed model repeated measures; MPNST: malignant peripheral nerve sheath tumour; MRI: magnetic resonance imaging; N/A: not applicable; NCI: National Cancer Institute; NF1: type 1 neurofibromatosis ; NIH: National Institutes of Health; NRS-11: numerical rating scale 11; ORR: objective response rate; PBMC: peripheral blood mononuclear cells; PN: plexiform neurofibromas; PedsQL: Pediatric Quality of Life Inventory; PFS: progression-free survival; PFTs: pulmonary function tests; PII: pain interference index; PR: partial response; PRO: patient reported outcomes; PROMIS: Patient-reported Outcomes Information System; HRQoL: quality of life; SAS: safety analysis set; TTP: time to progression; TTR: time to response.
Source: AstraZeneca Data on File (CSR, SPRINT protocol, SAP);[34, 38, 40] Gross et al. 2020.[18]

Selumetinib dosing strategy, continuation and discontinuation criteria

Selumetinib (25 mg/m^2 BSA BID) was administered in 28-day cycles, with no rest periods between treatment cycles. Efficacy evaluations were performed prior to starting a new cycle.[18, 38, 40] Patients could receive the next treatment cycle at the same dose unless they had experienced:[18, 38, 40]

1. Toxicities requiring dose modification, or
2. Disease progression, which required treatment discontinuation

If a patient experienced a toxicity requiring dose modification, selumetinib was withheld. Patients who were receiving a clear clinical benefit from selumetinib could continue treatment (at a reduced dose) if recovery from toxicity occurred within three months of stopping selumetinib. Patients who were not receiving a clear clinical benefit from selumetinib permanently discontinued from selumetinib treatment if a toxicity did not resolve to Grade 1 or lower within 21 days of stopping treatment.[18, 38, 40]

Patients with progressive disease (≥20% increase in neurofibroma volume ≤15 month before enrolment) could continue to receive selumetinib, as long as disease progression was not seen during treatment.[18, 38, 40]

For patients without progressive disease at study entry, treatment could be continued for a maximum of two years in the absence of a response. If a partial response was seen for these patients, treatment could continue unless subsequent disease progression was experienced, or the criteria for discontinuation of therapy were met.[18, 38, 40]

Patients removed from treatment after two years for reasons other than toxicity or progression were monitored. If PN volume increases of ≥15% were detected within approximately two years of stopping selumetinib, treatment with selumetinib could be restarted. In this case, treatment could continue as long as the PN remained stable or responsive.[38, 40]

Response criteria

A cut-off of ≥20% volume change was used to indicate PN progression or partial response to treatment across the primary and secondary endpoints of SPRINT Phase II Stratum I, and enabled investigators to categorise patients into different response definitions.[137]

The following response and progression definitions, as per the REiNS criteria which are widely used in NF1 PN clinical trials, were used in SPRINT Phase II Stratum I for the evaluation of primary and secondary endpoints:[38, 40]

- CR was defined as the disappearance of the target PN
- Partial response (PR) was defined as a decrease in the volume of the target PN by ≥20% compared with baseline. PR was considered unconfirmed (uPR) at its first detection and cPR when observed on consecutive restaging examinations at least three months apart
- Stable disease was defined as insufficient volume change to qualify for either PR or progressive disease

- Progressive disease was defined as an increase in volume of the target PN of ≥20% compared with baseline or, if an increase of ≥20% from best response if a patient had had a PR

In addition, the following response definitions were used:

- ORR was defined as the percentage of patients with CR or cPR in an intention-to-treat (ITT) analysis
    - BOR was defined as the best response recorded from the start of treatment until progression or the last evaluable volumetric MRI assessment in the absence of progression

External Control Data

NCI Natural History Study

The Natural History study was set up by the NCI to develop a better understanding and quantification of NF1 manifestations, to allow more sensitive endpoints to be developed for clinical studies and to allow for more effective treatment interventions for NF1. This study serves as an umbrella protocol for NCI POB's NF1 clinical study programme and uses volumetric MRI analysis to longitudinally monitor the growth of PN and other tumour and non-tumour-related manifestations in children and adults with NF1.[34] The primary objective of the NF1 Natural History study is to serve as an umbrella protocol for the ongoing NF1 clinical trials programme to longitudinally characterise and analyse NF1-related tumour and non-tumour manifestations, and to develop a better understanding of the biology of NF1-related manifestations.

The PN growth data from patients with NF1-related PN in the Natural History study was analysed, as collected up to October 2018, to provide supportive evidence and contextualisation for efficacy by serving as an external control for NF1-related PN growth and PFS data in SPRINT Phase II Stratum 1.[34]

The methodology for the Natural History study is described in Table C6. A subset of the Natural History study was used to form a cohort of NF1 PN patients age-matched to those in SPRINT Phase II Stratum I.[18, 34] Further details of the age-matched cohort are described in Section 9.4.3.

Table C6. Summary of methodology of the Natural History study

Study name	NCI Natural History Study of Patients with NF1 (NCT00924196)
Objective	To allow the longitudinal evaluation of individuals with NF1 for NF1-related tumour and non-tumour manifestations irrespective of whether they are currently enrolled in a treatment study or not, and to develop a better understanding of the biology of NF1-related manifestations
Location	US
Design	Longitudinal, observational, natural history study
Duration of study	Study is ongoing
Patient population	Children, adolescents, and adults with a confirmed clinical diagnosis of NF1 or a confirmed NF1 mutation
Sample size	157
Key inclusion criteria	**Age limit:**

	• Aged ≤35 years for all new patients • No upper age limit for patients previously enrolled in clinical trials at NIH, patients diagnosed with MPNST or with clinical concern for MPNST, or with infrequent or unusual NF1-related manifestations **Diagnosis of NF1:** • Diagnosis of NF1 using the NIH Consensus Conference criteria,[a] or have a confirmed NF1 mutation with analysis performed in a CLIA-certified laboratory **Prior treatment:** • Patients who have previously received medical or surgical intervention for NF1, or are currently receiving medical treatment or radiation for an NF1 manifestation, are eligible **Other:** • ECOG performance status ≤3 • Patients must be able to travel to the NIH for evaluations
Key exclusion criteria	• In the opinion of the investigator, if the patient is not able to return for follow-up visits or obtain required follow-up studies • In the opinion of the investigator, if the patient is not able to obtain an MRI scan
Intervention(s) and comparator(s)	N/A
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Baseline evaluation is carried out within the first six months of study entry. NF1 manifestations are longitudinally monitored with a frequency of every year to every three years, with the extent and timing of follow-up evaluations depending on the findings at baseline.
Statistical tests	N/A[b]
Primary and secondary outcomes (including scoring methods and timings of assessments)	Over 25 different evaluations were planned and as many of these as possible were intended to be performed on all of the individuals enrolled in the trial. However, it was not considered a protocol violation if certain assessments were not performed at a given time. The evaluations that were most relevant to NF1 PN included: • History physical examination with vital signs and phenotyping (at baseline, then every 12 months until 18 years, then every three years) • Pain evaluation[c] (at baseline, then every 12 months until 18 years, then every three years) • Volumetric MRI of PN (at baseline, then every 12 months until 18 years, then every three years) • Whole-body MRI to assess PN and MPNST burden (at baseline, then every three years and as clinically indicated) • Performance status (at baseline, then every 12 months until 18 years, then every three years) • Neuropsychological testing and QoL (at baseline, then every 12 months until five years of age, every three years for patients six years and older) • Physical activity questionnaires (at baseline)

Footnotes: [a]NIH Consensus Conference criteria for NF1 diagnosis are discussed in Section 8.1. [b]The statistical tests for the main Natural History study are not equivalent to the statistical analysis for the age-matched cohort, the only data presented within this submission. [c]Measures taken from patients aged six years and older, and parents of patients aged 6-18 years.
Abbreviations: CLIA: clinical laboratory improvement amendments; ECOG: European Cooperative Oncology Group; MRI: magnetic resonance imaging; MPNST: malignant peripheral nerve sheath tumours; N/A: not applicable; NCI: National Cancer Institute; NF1: type 1 neurofibromatosis; NIH: National Institutes of Health; PN: plexiform neurofibromas; QoL: quality of life.
Source: Gross et al. 2020;[18] ClinicalTrials.gov;[82] AstraZeneca Data on File (Natural History study protocol).[138]

Tipifarnib Study 01-C-0222

A Phase II randomised, controlled trial was designed to evaluate the safety and efficacy of the farnesyltransferase inhibitor, tipifarnib, in paediatric patients with NF1 and progressive PNs. The trial was designed with a placebo arm, to be used as a historical control for future studies of interventions for NF1 PN.[41] The details of this study are summarised in Table C7.

Table C7. Summary of methodology of tipifarnib study 01-C-0222

Study name	Tipifarnib (R115777) Study 01-C-0222 (NCT00021541)
Objective	To evaluate TTP on tipifarnib treatment vs placebo, defined as ≥20% PN volume increase, measured using volumetric MRI analysis
Location	US
Design	Randomised, cross-over, double-blind, placebo-controlled, Phase II trial
Duration of study	Eight years
Patient population	Patients aged 3–25 years with NF1 and unresectable, progressive PN
Sample size	60
Key inclusion criteria	**Age limit:** • Children and young adults aged ≥3 years and ≤25 years • Life expectancy ≥12 months **Diagnosis of NF1 PN:** • Clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity • PN were considered progressive if they had any of the following over the last two consecutive MRI scans or within ~1 year prior to trial evaluation: o ≥20% increase in PN volume, or o ≥13% increase in 2D measurement, or o ≥6% increase in 1D measurement **Prior treatment:** • Patients could enrol if they had previous surgery on the PN, provided it was measurable (≥3 cm in one dimension) • Patients must be able to undergo MRI • Time since prior therapy: o ≥6 weeks since radiotherapy o ≥4 weeks since chemotherapy o >30 days since therapy with an investigational agent • **Other:** o ECOG performance status 0–2

Key exclusion criteria	o Ongoing hormonal-, immuno- or chemotherapy directed at PN o Presence of optic glioma, malignant glioma, MPNST, or other cancer requiring treatment o Inability to return for follow-up visits
Intervention(s) and comparator(s)	**Intervention**: Tipifarnib (n=31) **Comparator**: Placebo (n=29)
Baseline differences	At enrolment, the median age and PN volume of participants randomised to the tipifarnib arm in Phase A were slightly greater compared with participants on the placebo arm. Further baseline differences between the two arms are described as part of the Appendix (Section 17.7.1).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	In Phase A of the trial, participants were followed on their first assigned treatment (tipifarnib or placebo) until progression. At this point, participants crossed over to the other arm (Phase B) and received the other treatment (placebo if their previously received tipifarnib and vice versa). Patients were monitored in the same manner during both trial phases until progression was documented on Phase B, at which point they were removed from the study. Two patients were lost to follow-up. The duration of follow-up was not reported.
Statistical tests	Comparison of TTP in participants receiving tipifarnib to participants receiving placebo during phase A was the primary analysis, and was used to estimate the sample size. In the absence of historical data for TTP based on 3D PN measurements, it was assumed that TTP for untreated PN would be six months. To detect an increase in the median TTP on Phase A, 30 participants per arm were required (six months with placebo to 12 months with tipifarnib with 80% power and a 1-tailed alpha ¼ 0.05). Kaplan–Meier analysis and log-rank statistics were used to compare TTP with tipifarnib vs placebo. The Kaplan–Meier analysis placed all participants who received treatment with placebo onto one curve and placing all those who received tipifarnib onto another curve, irrespective of the treatment phase. A large effect size was chosen, as only a substantial, clinically meaningful increase in the TTP on tipifarnib would justify the chronic and prolonged administration of an experimental agent to this young population with histologically benign tumours. PN growth rates were analysed using linear regression for each target PN to detect change in PN growth rate as a result of age, and paired results between phases (all participants who received treatment on both phase A and phase B) were compared using a 2-tailed Wilcoxon signed rank test. The growth rates of target PN and of nodular PN lesions were also compared with a 2-tailed Wilcoxon signed rank test. To evaluate for differences between the placebo and treatment arm at enrolment, a Cox model was constructed containing treatment arm, age, PN type (nodular vs typical), number of progressive PN documented at enrolment and number of PN known at enrolment.
Primary outcomes (including scoring methods and timings of assessments)	• To evaluate TTP, defined as ≥20% PN volume increase, measured using volumetric MRI analysis PN were assessed using volumetric MRI; images of up to three most clinically relevant target PN were performed prior to the start of Cycles 1, 4, 7 and 10, and then after every six cycles. Data were sent to the NCI for central analysis. Progression was determined by

	a PN volume increase of ≥20% in at least one PN compared with baseline on Phase A or Phase B.
Secondary outcomes (including scoring methods and timings of assessments)	• HRQoL for tipifarnib and placebo treated patients • Comparison of the acute and chronic toxicities experienced with tipifarnib and placebo treatment

Abbreviations: 1D: 1 dimensional; 2D: 2 dimensional; ECOG: European Cooperative Oncology Group; MPNST: malignant peripheral nerve sheath tumour; MRI: magnetic resonance imaging; NCI: National Cancer Institute; NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas; HRQoL: quality of life; TTP: time to progression.
Source: Widemann et al. 2014.[41]

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Data from SPRINT Phase II Stratum I can be found in a number of different published and unpublished sources, with each source covering different durations of follow-up. The data representing the longest periods of follow-up for each category of outcome are presented within this submission.

An overview of the primary data sources informing this submission are presented in Table C8. The sources are grouped by the category of data they include, and the organisation that conducted each biostatistical analysis is listed. Further details of these primary data sources are provided below the table, including the rationale for the choice of each data source and details of the corresponding periods of follow-up.

Table C8. Primary data sources for SPRINT Phase II Stratum I presented in this submission

Data category	Data source	Biostatistical analysis by
Efficacy: tumour volumetric responses	Gross et al. 2020[18]	NCI
Efficacy: clinical outcome measures	CSR[34]	AZ
Safety	CSR[34]	AZ
	90DSU[58]	AZ

Abbreviations: 90DSU: 90-day safety update; AZ: AstraZeneca; CSR: clinical study report; NCI: National Cancer Institute.
Source: Gross et al. 2020,[18] AstraZeneca Data on File (SRINT CSR),[34] AstraZeneca Data on File (90DSU).[58]

In June 2021, the NCI presented data from the most recent data cut-off for SPRINT Phase II Stratum I (27th February 2021), representing an additional two years of follow up, at the Children's Tumour Foundation conference.[66] This presentation was delivered after the clinical SLR searches were run, and therefore was not identified as part of the SLR. The oral presentation only included top-line efficacy and safety data and therefore has not been used a primary data source. However, results from this presentation have been referred to where relevant.

Efficacy: tumour volumetric responses

Analysis of PN volumetric data from SPRINT Phase II Stratum I has been performed by both AZ and the NCI, with results reported in the clinical study report (CSR) and Gross et al. 2020, respectively.[18, 34]

In 2020, Gross et al. published PN volumetric data from the 29th March 2019 SPRINT Phase II Stratum I data cut-off (DCO). The volumetric assessment of the MRI scans and the biostatistical analysis of the data included in the publication were all performed by the NCI.[18]

The volumetric data published in the Gross et al. 2020 manuscript represent a period of follow-up of three years since the start of selumetinib treatment, demonstrating the efficacy of selumetinib over a longer period of time and treatment exposure than data reported in the CSR. As such, the volumetric data from Gross et al. 2020 is reported within this submission.

Efficacy: clinical outcome measures

Clinical outcome measures are reported in both the CSR[34] and Gross et al. 2020[18] publication. The data reported in the CSR are from analyses by AZ, performed according to the statistical analysis plan (SAP),[34, 40] whereas the data reported in the Gross et al. 2020 publication are from analyses by the NCI.[18]

Whilst Gross et al. 2020 presents tumour volumetric data from a more recent DCO (29th March 2019) than the CSR (29th June 2018), results for clinical outcome measures were only reported up to pre-Cycle 13 (representing one year of treatment) within the Gross et al. publication (see Section 9.4.1). In contrast, the CSR reports data for clinical outcome measures up to pre-Cycle 25 (representing two years of treatment). Therefore, in order to present the longest duration of follow-up, the results for clinical outcome measures from the CSR have been reported within this submission.

Safety

Safety data from SPRINT Phase II Stratum I are presented in the CSR and 90-day safety update (90DSU) and have been analysed by AstraZeneca as per the SAP.[40] Safety data for the period up to the 29th June 2018 DCO are presented in the CSR. Additional safety data from the nine-month period between the 29th June 2018 DCO and 29th March 2019 DCO are presented in the 90DSU, which was provided to the FDA as agreed 90 days after the original New Drug Application, alongside safety data for the period up to 29th June 2018.[58]

Data from the 90DSU (29th March 2019 DCO) are included as the source of safety data, as they represent the longest period of follow-up available from the SPRINT Phase II Stratum I trial.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

As the SPRINT Phase II trial was a single arm study, in order to determine the comparative effectiveness of selumetinib vs established clinical management alone, comparisons to external controls have been made (see Section 9.4.1). These comparisons utilise data from two studies: the NCI Natural History study of NF1 (NCT00924196) and a RCT investigating tipifarnib treatment in patients with NF1 PN (NCT00021541).

The design and methodology of these three studies were very different, however, the methodologies used to carry out the analyses ensured the populations that were compared were well aligned, as described below.

Table C9 and Table C10 present the baseline patient and disease characteristics, respectively, for SPRINT Phase II Stratum I, and the Natural History study and tipifarnib Study 01-C-0222 patient populations that were used for the comparative effectiveness analyses. Baseline characteristics for SPRINT Phase II Stratum I are reported as per the CSR.[34]

Table C9. Baseline patient characteristics in SPRINT Phase II Stratum I and external comparator studies

Patient characteristics	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
Age, years median (range)	[redacted]	7.8 (3.0–17.0)	8.2 (3–17.7)
Age, years mean (SD)	[redacted]	NR	NR
Sex, n (%)			
Male	[redacted]	57 (61)	14 (48)
Female	[redacted]	36 (39)	15 (52)
Race, n (%)			
White	[redacted]	72 (77)	NR
Black or African American	[redacted]	7 (8)	NR
Asian	[redacted]	1 (1)	NR
Unknown	[redacted]	13 (14)	NR
Ethnic group, n (%)			
Not Hispanic or Latino	[redacted]	NR	NR
Hispanic or Latino	[redacted]	NR	NR
Unknown	[redacted]	NR	NR
Not reported	[redacted]	NR	NR
Height, cm median (range)	[redacted]	NR	NR
Weight, kg median (range)	[redacted]	NR	NR
BSA, m^2 median (range)	[redacted]	NR	NR
BSA, m^2 mean (SD)	[redacted]	NR	NR

Abbreviations: BSA: body surface area; NR: not reported; PN: plexiform neurofibromas; SD: standard deviation.
Source: Gross et al. 2020 (DCO 29th March 2019);[18] AstraZeneca Data on File (SRINT CSR);[34] Widemann et al. 2014.[41]

Table C10. Baseline disease characteristics in SPRINT Phase II Stratum I and external comparator studies

Disease characteristics	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
Target PN volume at baseline, mL median (range)	[redacted]	354 (3.7–4895.0)	316 (39.6–4896)
Time from diagnosis of NF1 to start of treatment, years median (range)	[redacted]	N/A	NR
Time from diagnosis of PN to start of treatment, years median (range)	[redacted]	N/A	NR
Target PN status, n (%)			
Progressive[c]	[redacted]	NR	29 (100)
Unprogressive	[redacted]	NR	0 (0)
Unknown	[redacted]	NR	0 (0)
Target PN location, n (%)[d]			
Neck and trunk	[redacted]	13 (14)	NR
Neck and chest	[redacted]	NR	9 (31)
Trunk and limbs	[redacted]	17 (18)	3 (10)
Head only	[redacted]	13 (14)	NR
Face	[redacted]	NR	3 (10)
Head and neck	[redacted]	5 (5)	4 (14)
Trunk only	[redacted]	36 (39)	NR
Limbs only	[redacted]	8 (9)	1 (3)
Whole body	[redacted]	1 (1)	NR
Target PN morbidity assessment, n (%)			
Pain	[redacted]	NR	NR
Disfigurement	[redacted]	NR	NR
Motor dysfunction	[redacted]	NR	NR
Airway	[redacted]	NR	NR
Bowel and/or bladder dysfunction	[redacted]	NR	NR
Orbital (vision)	[redacted]	NR	NR
Other dysfunction	[redacted]	NR	NR
Number of target PN morbidities, median (range)	[redacted]	NR	NR

Footnotes: [a]Data available for 48/50 patents enrolled in the trial. [b]Data available for 45/50 patients enrolled in the trial. [c]Progressive PN status is defined as a ≥20% increase in neurofibroma volume ≤15 month before enrolment. [d]Exact descriptions of PN location used in each study have been reported here.
Abbreviations: NF1: Type 1 neurofibromatosis; NR: not reported; PN: plexiform neurofibromas.
Source: Gross et al. 2020;[18] AstraZeneca Data on File (SRINT CSR);[34] Widemann et al. 2014.[41]

SPRINT Phase II Stratum I vs Natural History Study

As previously discussed in Section 9.4.1, non-randomised comparisons vs external controls were performed in order to determine the comparative effectiveness of selumetinib vs relevant comparators. Given that SPRINT Phase II Stratum I was a single arm study due to the ethical and practical reasons for not conducting an RCT in this patient group, this comparison was considered an appropriate and necessary analysis.

There are some important similarities which justify the comparison of PN volumetric data between SPRINT Phase II Stratum I and the Natural History study. Tumour volumetric MRI was used to assess PN growth over time, and the criteria of a ≥20% increase in PN volume was used to define PN progression, in both SPRINT Phase II Stratum I and the Natural History study. In addition, both studies were carried out by the NCI and used the National Institutes of Health Clinical Centre in Maryland, USA as a trial site. Due to this methodological overlap, these trials are expected to be broadly comparable in the way procedures were carried out.

Despite these similarities between the two studies, there were also differences in study design and methodologies worth noting. The Natural History study was an observational study aiming to investigate patients with NF1 over time, in comparison to the interventional design of SPRINT Phase II Stratum I. The Natural History study therefore focused on collecting information on a range of NF1- and PN-associated disease characteristics and morbidities over time, rather than assessing only outcomes relevant to selumetinib treatment. The trial population of the Natural History study included, but was not limited to, paediatric patients with NF1 PN, whereas SPRINT Phase II Stratum I enrolled only paediatric patients with NF1 PN.

To account for differences in study design and methodology, a cohort of 93 patients from the Natural History study with a maximum duration of follow-up of 3.2 years was selected as a comparison population; this cohort was age-matched to SPRINT Phase II Stratum I patients, to allow for a more robust comparison by eliminating the confounding factor of age. The age-matched cohort included patients aged 3–18 years who had a least two volumetric MRI scans, with the first scan performed between the ages of 3–18 years (considered baseline). The age-matching approach allowed alignment with the enrolled age population and evaluation time of the baseline volumetric scan in the SPRINT Phase II Stratum I.[18, 34]

In addition, in order to directly compare the data in the age-matched cohort to the data from SPRINT Phase II Stratum I, a maximum follow-up duration of 3.2 years was selected for the Natural History age-matched cohort, to be equal to the maximum duration of follow-up in Stratum I.[18, 34]

SPRINT Phase II Stratum I vs tipifarnib Study 01-C-0222

The tipifarnib Study 01-C-0222 was an RCT, designed with a placebo arm which could be used as a historical control for future studies of interventions for NF1 PN.[41] This is in comparison to SPRINT Phase II Stratum I, which was a single arm open-label study. Only the 29 patients enrolled on the placebo arm of tipifarnib Study 01-C-0222 were used as a comparator to the SPRINT Phase II Stratum I data.

Tumour volumetric MRI was used to assess PN growth over time in both studies, and the criteria of a ≥20% increase in PN volume was used to define disease progression; the methods for assessing PN growth are therefore broadly similar between the two studies.

SPRINT Phase II Stratum I and tipifarnib Study 01-C-0222 enrolled different patient populations and these differences were therefore accounted for in the analysis methodology. All patients recruited to the tipifarnib Study 01-C-0222 were required to have unresectable PN, aligning with the definition of inoperability used in SPRINT Phase II Stratum I inclusion criteria. However, patients in the tipifarnib Study 01-C-0222 were not required to have symptomatic PN, unlike patients enrolled on SPRINT Phase II Stratum I; this is likely to have led to differences in the characteristics of the target PN examined in the two studies. Additionally, as only patients with progressive PN were enrolled in tipifarnib Study 01-C-0222, comparisons were made both to the 21/50 (42%) patients from SPRINT Phase II Stratum I with progressive PN at study entry, and to the full cohort of 50 patients enrolled in SPRINT Phase II Stratum I.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Not applicable.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

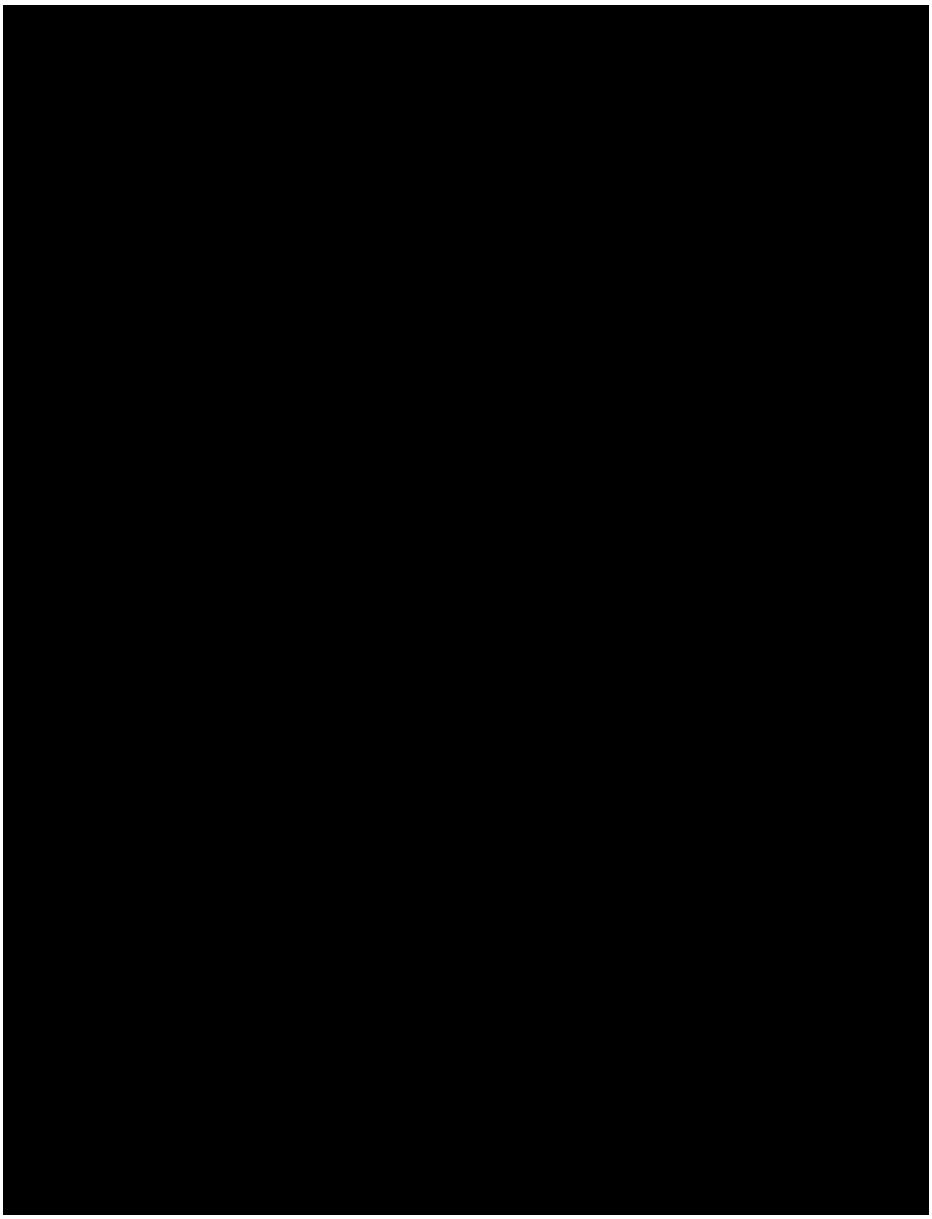
A total of 50 patients were recruited to SPRINT Phase II Stratum I. As described in Section 9.4.3, SPRINT was a single arm study, therefore all patients were allocated to receive selumetinib. Table C11 and Figure C2 show that [redacted] remained on study treatment up to the 90DSU DCO (29th March 2019).[58]

Table C11. Patient disposition of SPRINT Phase II Stratum I

Patient disposition	Selumetinib
Recruited, n	50
Treated with selumetinib, n (%)	[redacted]
On treatment at DCO, n (%)	[redacted]
Discontinued study treatment, n (%)	[redacted]
Number of treatment cycles, median (range)	[redacted]

Abbreviations: DCO: data cut-off.
Source: 90DSU;[58] Gross et al. 2020,[18]

Figure C2. Patient disposition in SPRINT Phase II Stratum I



Abbreviations: DCO: data cut-off.
Source: 90DSU.[58]

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

In the period up to the 29th March 2019 DCO, representing the longest duration of follow-up, [redacted] patients discontinued selumetinib. The reasons for discontinuation are presented in Table C12 (data reported from the 90DSU).[58]

[redacted]

[redacted] Patients who achieved a PR of their PN and subsequently met the criteria for disease progression, but in whom their PN had not increased ≥20% from baseline, were eligible for re-treatment if they had discontinued treatment prior to this protocol amendment.[58]

Table C12. Proportion of patients who discontinued and terminated study treatment in SPRINT Phase II Stratum I

Reason for discontinuation	Selumetinib (N=50), n (%)
Discontinued study treatment	[redacted]
Adverse event	[redacted]
Disease progression	[redacted]
Investigator discretion	[redacted]
Treatment period completed	[redacted]
Patient not willing to continue future treatment	[redacted]
Severe non-compliance to protocol	[redacted]
Terminated study treatment	[redacted]
Voluntary discontinuation	[redacted]
Lost to follow-up	[redacted]
Other	[redacted]

Source: 90DSU.[58]

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C13 and C14.

Table C13. Critical appraisal of randomised control trials: tipifarnib Study 01-C-0222

Study name	Tipifarnib Study 01-C-0222	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Randomisation occurred centrally via a random allocation sequence that was randomly generated by a computer program, written in house.
Was the concealment of treatment allocation adequate?	Yes	The trial was double-blinded, so neither the participant nor treating physician were made aware of the treatment allocation.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	The median age and PN volume of participants randomised to the tipifarnib arm on phase A were slightly greater compared with participants on the placebo arm. There was also a higher number of PN in the placebo group but it is not clear whether

		this is statistically significant. There was no significant difference in sex by arm.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Participants and outcome assessors were blinded to treatment allocation. No information was provided on whether the care providers were aware of treatment allocation, however, the study states the randomisation sequence was provided on a paper list only to the pharmacy, suggesting caregivers were not aware of treatment allocation.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not clear	13 participants were removed from the study in phase A and 16 participants were removed from the study prior to or during phase B, however no detail on the proportion of these patients who were in the tipifarnib group or placebo group was provided. It is therefore unclear whether drop-out rates were similar between treatment groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No evidence to suggest authors measured more outcomes than reported.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Analysis method not explicitly written, but patient number reported in study outcomes suggest a per protocol approach was taken.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Abbreviations: CRD: Centre for Reviews and Dissemination; ITT: intention-to-treat; N/A: not applicable; PN: plexiform neurofibroma.
Source: Widemann et al. 2014[41]

Table C14. Critical appraisal of observational studies: NCI Natural History study

Study name	NCI Natural History study	
Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Patients with NF1 and at least one PN were enrolled, inclusion and exclusion criteria clearly defined.
Was the exposure accurately measured to minimise bias?	Yes	Objective measurements were used.
Was the outcome accurately measured to minimise bias?	Yes	Efficacy and safety outcomes measured using objective criteria (e.g. specified PN volume change, systematic determination of morbidities based on clinical notes) and according to study protocol.
Have the authors identified all important confounding factors?	Yes	These have been identified and measured at baseline.

Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Insufficient information on how baseline confounding factors were taken into account in outcome measures.
Was the follow-up of patients complete?	No	Patients were measured every 12 months until they were 18 years old, then every 1–3 years after. Patients were included in the analysis if they had at least seven years of clinical data from at least two different timepoints available. The study is ongoing.
How precise (for example, in terms of confidence interval and p values) are the results?	Not clear	Confidence intervals stated for most outcomes (to two decimal places) and clinically important results were ascertained by using both the rank sum test P-values (to three decimal places) and effect sizes; single-arm design means groups cannot be compared.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: CASP: Critical Appraisal Skills Programme; N/A: not applicable; NCI: National Cancer Institute; NF1: type 1 neurofibromatosis; PN: plexiform neurofibroma.
Source: Gross et al. 2018[11]

Table C15. Critical appraisal of observational studies: SPRINT Phase II Stratum I

Study name	SPRINT Phase II Stratum I	
Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Patients with and without NF-related complications were enrolled, inclusion and exclusion criteria clearly defined. The study sponsor had no role in recruitment.
Was the exposure accurately measured to minimise bias?	Yes	Objective measurements used.
Was the outcome accurately measured to minimise bias?	Yes	Efficacy and safety outcomes measured using objective criteria (e.g. RECIST; CTCAE) and according to study protocol.
Have the authors identified all important confounding factors?	Yes	These have been identified and measured at baseline.
Have the authors taken account of the confounding factors in the design and/or analysis?	Unclear	Insufficient information.
Was the follow-up of patients complete?	No	Three years of follow-up is complete, study is ongoing.
How precise (for example, in terms of confidence interval and p values) are the results?	Unclear	Confidence interval stated for PR but not all outcomes; single-arm design means groups cannot be compared.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; N/A: not applicable; NF: neurofibromatosis; RECIST: Response evaluation criteria in solid tumours.
Source: Gross 2020[18]

9.6 Results of the relevant studies

Summary of Section C9.6

Primary outcome: objective response rate

- 68% of children in SPRINT Phase II Stratum I had a cPR to selumetinib treatment, representing a ≥20% reduction in target PN volume from baseline, compared to no patient in the age-matched Natural History study cohort with ≥20% decrease in PN volume over an equivalent time period[18]

Secondary outcomes: tumour volumetric responses

- 90% of patients treated with selumetinib had a BOR of reduction in PN volume from baseline, and 74% of patients experienced ≥20% reduction in PN volume at BOR[18]
- No patients receiving selumetinib displayed a PN growth rate of ≥20% per year, compared to 43% of patients with a PN growth rate of >20% per year in the age-matched cohort. The median change in PN volume in patients treated with selumetinib was a 23% decrease, compared to a 77% increase observed in the age-matched cohort,[18] emphasising the extent of tumour reduction that can be achieved with selumetinib
- Children in the SPRINT trial had a higher probability of PFS over 3 years compared to the Natural History study age-matched cohort (84% vs 15%), [redacted] (89% vs 21%)[34]

Secondary outcomes: clinical outcome measures

- In addition to positive PN volumetric responses, patients treated with selumetinib experienced stabilisations and improvements across a range of clinical outcome measures; [redacted][34]
- Based on self- and parent-reported PedsQL total scores, up to [redacted]
- Selumetinib treatment led to a clear reduction in pain intensity, and selumetinib-treated patients and their parents further reported clinically meaningful improvements in PN-related pain interference with daily functioning[34]
- Selumetinib treatment led to clinically meaningful improvements in mobility, range of motion and strength, in particular for PN-related body quadrants. Further benefits of treatment with selumetinib were seen with regards to maintaining airway function and as improvements in disfigurement[34]

Secondary outcome: global impression of change

- For both self-reported and parent-reported GIC, [redacted]

[redacted][34]

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

The clinical efficacy results from the SPRINT Phase II Stratum I include:

- The primary outcome of ORR to selumetinib treatment (Gross et al. 2020),[18] as presented in Table C16 below
- The secondary outcomes for tumour volumetric responses (Gross et al. 2020),[18] as presented in Table C16 below
- The secondary outcomes for clinical outcome measures (SPRINT CSR),[34] as presented in Table C19
- The secondary outcome of global impression of change (SPRINT CSR),[34] as presented in Table C17, and Figure C13

Propensity score analyses were also explored for the non-randomised comparison of PFS for selumetinib in SPRINT Phase II Stratum I vs the Natural History study, with results presented in Section 9.8.1.

Table C16. Summary of tumour volumetric results

Tumour volumetric outcome measure	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
Primary outcome			
ORR (%)	68	0	N/A
Secondary outcomes			
BOR			
BOR of reduction in PN volume from baseline (%)	90	N/A	N/A
≥20% reduction in PN volume at BOR (%)	74	N/A	N/A
Duration of response	8 cycles	N/A	N/A
PN growth rate			
Patients with a PN growth rate >20% per year, % (n)	0 (0)	43 (40)	N/A
Median change in PN volume, between baseline and most recent MRI, % (range)	-23 (-55.1 – +30)	+77 (-40 – +1429)	N/A
PFS			

Median PFS, years	Not reached[a]	1.3 (1.1–1.6)	N/A
Probability of PFS at 3 years, %	84	15	N/A
Probability of PFS at 2 years, %	[redacted]	N/A	21

Footnotes: [a]The median PFS has not yet been reached, with only 12% of patients experiencing disease progression (6/50).[b]To allow for comparison to the placebo arm of the tipifarnib study, these values are based on *21 patients with progressive PN in the 18 months prior to enrolment* of SPRINT Phase II Stratum I. This comparison is discussed in detail later on in this section.[34]
Abbreviations: BOR: best objective response; CI: confidence interval; MRI: magnetic resonance imaging; N/A: not applicable; ORR: objective response rate; PFS: progression-free survival; PN: plexiform neurofibromas.
Source: Gross et al. 2020;[18] *Widemann et al. 2014;*[41] AstraZeneca Data on File (SPRINT CSR).[34]

Primary efficacy outcome: objective response rate

Results from Gross et al. 2020 are presented here for the primary outcome.[18]

The primary outcome measure of the SPRINT Phase II Stratum I was ORR to selumetinib, defined as the rate of confirmed PR and CR, using volumetric MRI analysis.[38] The majority of children, 68% (34/50), had a cPR to selumetinib treatment, representing a ≥20% reduction in target PN volume from baseline.[18] This result was consistent with the finding from SPRINT Phase I trial (cPR of 71%).[39] In contrast, none of the age-matched patients in the NCI Natural History study had a ≥20% reduction in tumour volume over the same time period (3 years);[18] Selumetinib treatment therefore benefits patients through the reduction in volume of symptomatic PN, which does not generally occur in the absence of disease-modifying treatment.[11, 18] Tumour size reduction of any extent is uncommon in this disease setting, demonstrating the step-change in clinical efficacy provided by selumetinib.

Age at enrolment, the volume and progression status of the target PN at baseline, and the location of the target PN, could not be used to determine whether a patient would have a PR.[18]

Secondary outcomes: tumour volumetric responses

Results from Gross et al 2020[18] are presented here for the secondary outcomes, unless otherwise stated.

PN growth rate

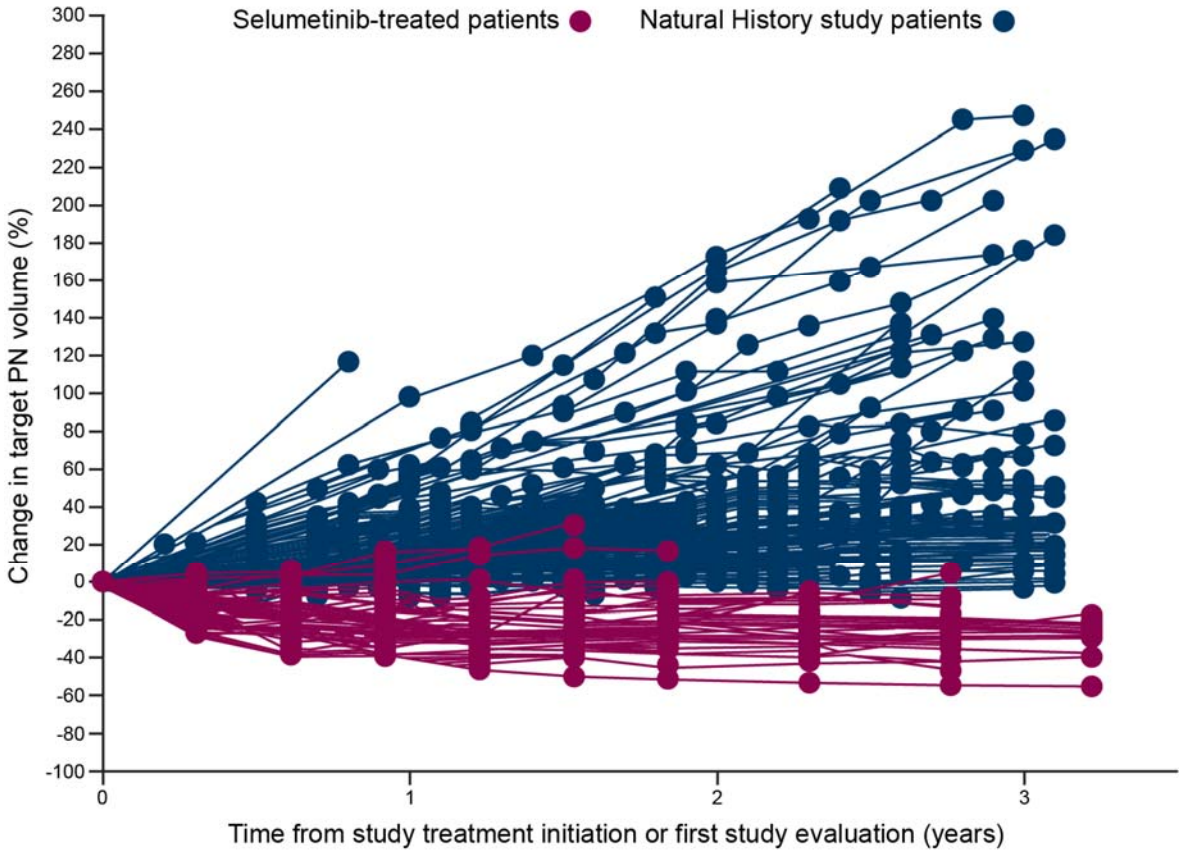
Selumetinib demonstrated clear efficacy in reversing PN volume growth, or stabilising PN growth, when compared with the Natural History study age-matched cohort, for the entirety of the three-year follow-up period (Table C17 and Figure C3). No patients receiving selumetinib displayed a PN growth rate of ≥20% per year (range -27.0%–19.8% per year), compared with 43% of patients in the age-matched cohort. The median change in PN volume in patients treated with selumetinib was a 23% decrease, compared to a 77% increase observed in the age-matched cohort.[18]

Table C17. Naïve comparison of SPRINT Phase II Stratum I to Natural History age-matched cohort for PN growth rate

Measure	SPRINT Phase II Stratum I (N=50)	Natural History age-matched cohort (N=93)
PN growth rate		
Patients with a PN growth rate ≥20% per year, % (n)	0 (0)	43 (40)
Median change in PN volume, between baseline and most recent MRI, % (range)	-23 (-55.1–+30)	+77 (-40–+1429)

Abbreviations: MRI: magnetic resonance imaging; PN: plexiform neurofibromas.
Source: Gross et al. 2020.[18]

Figure C3. Percentage change in target PN volume during selumetinib treatment in SPRINT Phase II Stratum I compared to an age-matched Natural History study control cohort



Abbreviations: PN: plexiform neurofibromas.
Source: Gross et al. 2020.[18]

Progression-free survival (PFS)

Median PFS was not reached in SPRINT Phase II Stratum I at DCO 29th March 2019 (Table C18). Based on the Kaplan-Meier curves, there was a continued divergence in PFS between patients receiving selumetinib in SPRINT Phase II Stratum I and patients in the Natural History Study age-matched cohort, over the duration follow-up period (Figure C4). At three years, 84% of

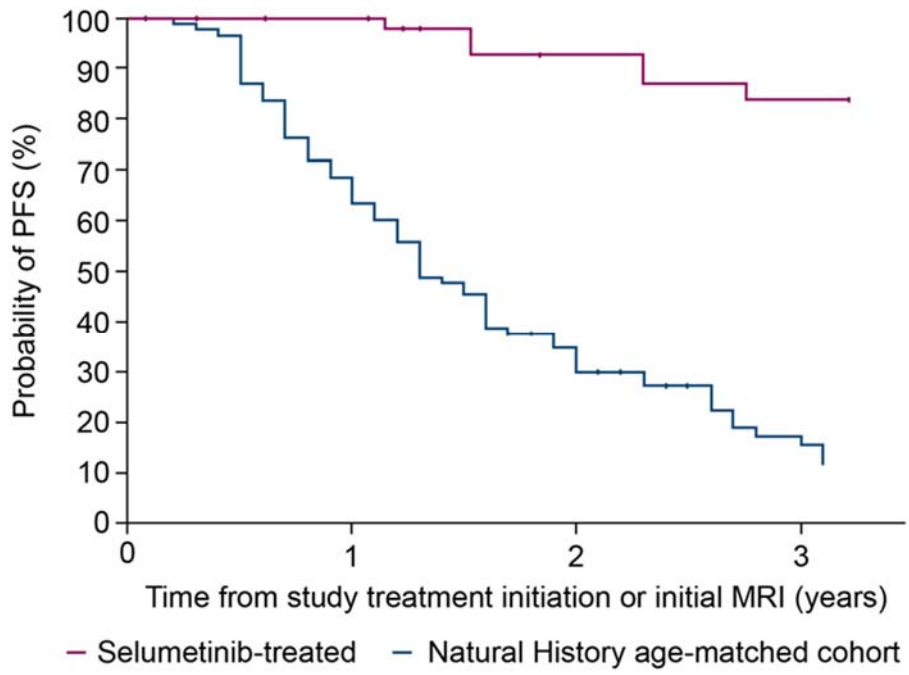
patients in SPRINT remained progression-free, compared with 15% in the Natural History age-matched cohort.[18] Selumetinib therefore offers significant benefits to patients, through prevention of PN volume growth and therefore the prevention of disease progression.

Table C18. Naïve comparison of SPRINT Phase II Stratum I to Natural History age-matched cohort for PFS

Measure	SPRINT Phase II Stratum I (N=50)	Natural History age-matched cohort (N=93)
PFS (over 3.2 years of follow-up)		
Median PFS, years (95% CI)	N/A[a]	1.3 (1.1–1.6)
Probability of PFS at 3 years, %	84	15

Footnotes: [a]The median PFS has not yet been reached, with only 12% of patients experiencing disease progression (6/50).
Abbreviations: CI: confidence interval; MRI: magnetic resonance imaging; N/A: not applicable; PFS: progression-free survival.
Source: Gross et al. 2020.[18]

Figure C4. PFS during selumetinib treatment in SPRINT Phase II Stratum I compared to the age-matched Natural History study control cohort



Abbreviations: MRI: magnetic resonance imaging; PFS: progression-free survival.
Source: Gross et al. 2020.[18]

An additional naïve comparison was conducted by AstraZeneca to compare the results of the SPRINT Phase II Stratum I study and external control data from the placebo arm of the tipifarnib Phase II Study 01-C-0222.[34, 41] Given that this analysis was conducted by AstraZeneca, data from the CSR were used for this evaluation.[34] As only patients with progressive PN were enrolled in Study 01-C-0222, only patients from SPRINT Phase II Stratum I with progressive PN were used for the comparison.[18]

As ORR was not assessed in the tipifarnib placebo arm, the secondary endpoint from SPRINT, PFS, was assessed in this comparison. Based on the 29th June 2018 DCO, of the patients included in SPRINT Phase II Stratum I, [redacted] patients had progressive PN in the 18 months prior to enrolment. Figure C5 shows that the probability of remaining without progression at 2 years was reported to be 21% (95% CI 7.7–37.8) for patients receiving placebo in the tipifarnib trial, compared with [redacted] for the subgroup of patients with progressive PN at enrolment receiving selumetinib in SPRINT. Selumetinib is therefore effective in preventing disease progression in symptomatic, inoperable PN which are actively growing.[34] These findings were consistent with the Natural History study comparisons presented above (Figure C5 and Table C18).

Figure C5. PFS during selumetinib treatment in SPRINT Phase II Stratum I vs placebo arm of tipifarnib Study 01-C-0222 (patients with progressive PN only)

Footnote: DCO for SPRINT data: 29th June 2018. Includes patients with progressive disease in the 18 months prior to enrolment from SPRINT Phase II Stratum I, as all patients in the tipifarnib Study 01-C-0222 had progressive disease. PFS was defined as the time from study treatment/placebo initiation until the pre-Cycle/date of objective progression or death (by any cause in the absence of progression) for SPRINT Phase II Stratum I/placebo arm of tipifarnib Study 01-C-0222, respectively. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable volumetric MRI assessment known to be non-progression.
Abbreviations: DCO: data cut-off; MRI: magnetic resonance imaging; NA: not applicable; PFS: progression-free survival; PN: plexiform neurofibromas.
Source: AstraZeneca Data on File (SPRINT CSR).[34]

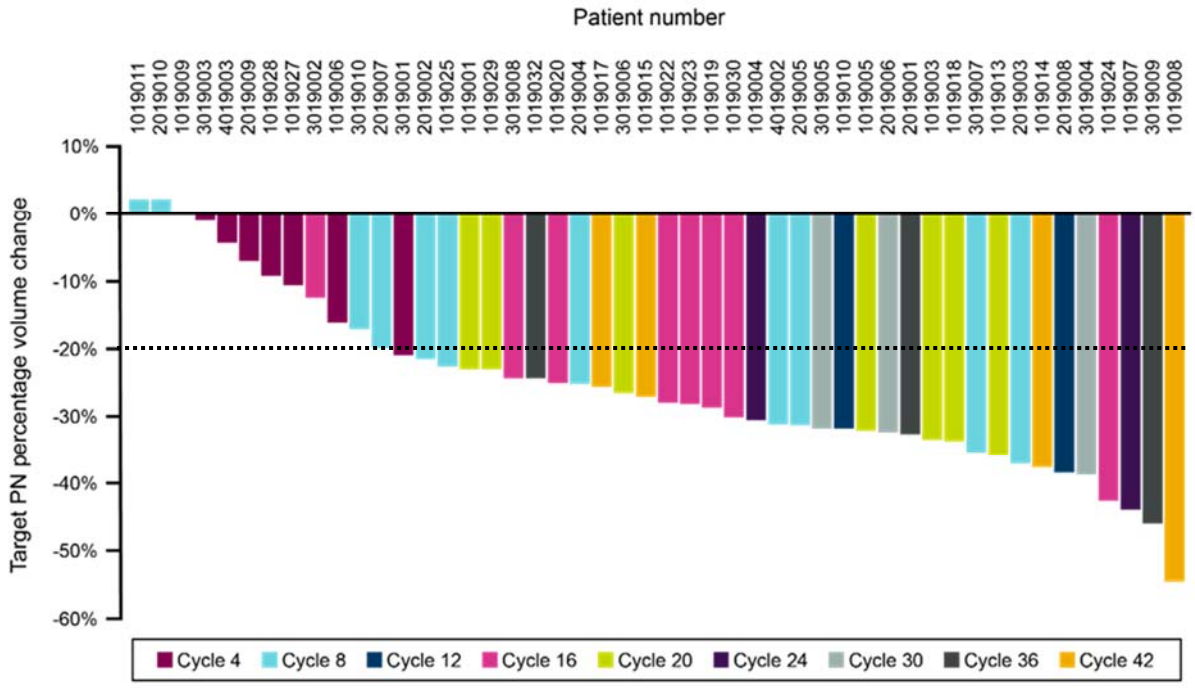
Best objective response

Patients treated with selumetinib, including young children for whom the highest PN growth rates are generally observed, experienced reductions or stabilisation in the volume of their symptomatic, inoperable PN. This is in contrast to the unpredictable and uncontrolled growth experienced by patients enrolled on the Natural History study; a 77% increase in volume from baseline was observed in the age-matched Natural History study cohort.[11, 18]

The majority of patients (45/50; 90%) treated with selumetinib in SPRINT Phase II Stratum I had a BOR of reduction in PN volume from baseline, and 74% (37/50) of patients experienced ≥20% reduction in PN volume at BOR (confirmed or unconfirmed PR). For most of these patients

(35/50; 70%), the ≥20% reduction in target PN volume from baseline was confirmed on consecutive examinations at least 3 months apart. No patients had a BOR of disease progression. The median change in PN volume at best response was -27.9% (range -55.1–2.2), showing a substantial reduction in volume.[18] A waterfall plot showing the best volumetric response for each target PN, and the cycle during which this best response was achieved, is presented below (Figure C).[18]

Figure C6. Best volumetric response from baseline in target PN volume in SPRINT Phase II Stratum I



Footnotes: The cut-off for partial response, a ≥20% reduction in PN volume, is indicated with the dotted line.
Abbreviations: PN: plexiform neurofibromas.
Source: Gross et al. 2020.[18]

Duration of response

The median time to initial response in SPRINT Phase II Stratum I was 8 cycles (range 4–20), and the median time to best response was 16 cycles (range 4–36). Of the 35 patients who had confirmed PR to selumetinib, 28 (80%) had a durable response to selumetinib treatment, defined as a response lasting for more than one year. This demonstrates that selumetinib treatment results in durable reductions in the volume of symptomatic, inoperable PN in paediatric patients, providing long-term benefit by preventing uncontrolled tumour growth over a number of years.[18]

Secondary outcomes: clinical outcome measures

Given that NF1 PN is a heterogenous disease with morbidity and severity dependent on both the size and location of the PN, it is important to capture the impact of selumetinib using a variety of tools. Results from the SPRINT CSR are presented in this section for the clinical outcome measures.[34] Clinical outcome assessments performed in SPRINT Phase II Stratum I investigated the impact of selumetinib on HRQoL and key PN-associated morbidities (see Section 6.1 for a description of the burden of these morbidities in the absence of disease-modifying treatment).

The numbers of patients eligible to be evaluated through each assessment are summarised in Figure C7. Table C19 presents a summary of the results from baseline to pre-Cycle 25 for each assessment, including the number of patients assessed, as not all eligible patients completed each assessment.[39]

Key results from the assessments of HRQoL, pain, motor function, airways and disfigurement are discussed in further detail below. Changes in clinical outcome measures from baseline are reported for the pre-Cycle 13 (12 months of selumetinib treatment) and pre-Cycle 25 (2 years of selumetinib treatment) assessments.[34] Pre-Cycle 13 was identified as a critical time point for evaluation based on findings of Phase I of the SPRINT trial, in which the majority of patients who experienced a response did so within the first year of selumetinib treatment.[39] As described in Section 9.4.1, the results were analysed by descriptive statistics, MMRM or CMTs.

Figure C7. Number of patients at baseline eligible to be evaluated for each clinical outcome assessment in the SPRINT Phase II Stratum I trial

Footnotes: N numbers refer to the number of patients eligible to be assessed for each outcome measure. Assessments for pain and HRQoL were completed irrespective of patients' baseline PN-associated morbidities. All other assessments were collected only from patients with those morbidities at baseline. Not all eligible patients completed each assessment.
Abbreviations: 6MWT: six-minute walk test; AHI: apnoea hypopnoea index; DVQ: dysfunctional voiding questionnaire; FEV: forced expiratory volume; GIC: global impression of change; HRQoL: health-related quality of life; NRS-11: numerical rating scale 11; PedsQL: Pediatric Quality of Life Inventory; PII: Pain Interference Index; PROMIS: Patient-reported Outcomes Measurement Information System.
Source: Adapted from AstraZeneca Data on File (SPRINT CSR).[34]

Table C19. Functional and PRO assessments of PN-associated morbidities

Outcome measure	Pre-Cycle 13 assessment completion	Pre-Cycle 25 assessment completion	Overall results
HRQoL			
PedsQL	Self-report: [redacted] Parent-report: [redacted]	Self-report: [redacted] Parent-report: [redacted]	[redacted] indicating that selumetinib results in sustained improvements in patient HRQoL
Pain			
NRS-11	Physician-selected target tumour pain: [redacted]	Physician-selected target tumour pain: [redacted]	Reduction in PN-related pain intensity for self-selected pain, target PN pain, overall PN pain and other pain, [redacted]
PII	Self-report: [redacted] Parent-report: [redacted]	Self-report: [redacted] Parent-report: [redacted]	Overall improvement from baseline in self-reported and parent-reported PII scores [redacted], demonstrating that selumetinib reduces pain interference
Motor function			
PROMIS® mobility	Self-report: [redacted] Parent-report: [redacted]	Self-report: [redacted] Parent-report: [redacted]	[redacted]
PROMIS® upper extremity	Self-report: [redacted] Parent-report: [redacted]	Self-report: [redacted] Parent-report: [redacted]	[redacted]
Strength (manual muscle test)	[redacted]	[redacted]	[redacted]
Range of motion	[redacted]	[redacted]	[redacted]
Grooved pegboard	[redacted]	Patients with unilateral upper body PN: [redacted]	Patients with unilateral upper body PN [redacted]. Patients with PN affecting both upper body quadrants

		Patients with bilateral upper body PN[redacted]	[redacted]
Grip strength and key pinch	[redacted]	[redacted]	Grip strength showed [redacted] Key pinch [redacted]
Leg length disparity	[redacted]	[redacted]	[redacted]
Airway function			
AHI (sleep study)	[redacted]	[redacted]	[redacted]
$FEV_1/FEV_{0.75}$	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted]
R_5	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	NR	[redacted]
R_{20}	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted]
Bowel/bladder function			
DVQ	Self-report: NR Parent-report: [redacted]	Self-report: NR Parent-report: [redacted]	[redacted] however, the confidence intervals were wide. Due to insufficient data at baseline ([redacted]), it was not possible to evaluate mean change for self-report scores

Visual function			
Visual acuity	[redacted] ([redacted]patients with enucleation of the affected eye or vision limited to light perception and position or worse were excluded from this evaluation)	NR	[redacted]
Amount of exophthalmos	[redacted]	NR	[redacted]
Disfigurement			
Photographs	NR	NR	There was no formally planned method for assessing changes in disfigurement. Many patients and parents reported subjective improvement in appearance
Other			
6MWT	[redacted]	[redacted]	[redacted]

Footnotes: Domains which are underlined are reported in further detail in this section.
Abbreviations: 6MWT: six-minute walk test; AHI: apnoea-hypopnoea index; DVQ: dysfunctional voiding questionnaire; FEV: forced expiratory volume; NR: not reported; NRS-11: numerical rating scale 11; PedsQL: Pediatric Quality of Life Inventory; PII: Pain Interference Index; PN: plexiform neurofibromas; PRO: patient-reported outcome; PROMIS: Patient-Reported Outcomes Measurement Information System.
Source: AstraZeneca Data on File (SPRINT CSR);[34] Gross et al. 2020.[18]

Health-related quality of life

Overall, a trend of improvement in self- and parent-reported HRQoL scores was seen over each measurement cycle, based on mean change from baseline in both PedsQL total score and domain scores, as shown in Figure C8 and Figure C9. Improvements were maintained across all domain scores of the PedsQL.

As described in Section 7.1, PN have a substantial negative impact on HRQoL in NF1 PN patients through the burden of morbidities, including pain, disfigurement or motor dysfunction.[19, 25, 26] Given that PN growth is associated with an increase in morbidity and decrease in HRQoL,[11] an association between the PN volume stabilisations and reductions seen with selumetinib treatment and the corresponding improvements in patient HRQoL.

Figure C8. Mean change from baseline in PedsQL self-reported scores

Footnotes: N=34. Children ages 8 to 18 years of age at enrolment completed self-report measures of the PedsQL.
Abbreviations: CI: confidence interval. PedsQL: Paediatric Quality of Life Inventory.
Source: AstraZeneca Data on File (SRINT CSR).[34]

Figure C9. Mean change from baseline in PedsQL parent-reported scores

Footnotes: N=50. Parents or legal guardians of children from 2 to 18 years of age at enrolment completed the parent proxy measures of the PedsQL.
Abbreviations: CI: confidence interval. PedsQL: Paediatric Quality of Life Inventory.
Source: AstraZeneca Data on File (SRINT CSR).[34]

A mixed model repeated measures (MMRM) analysis of change from baseline in PedsQL total score was performed, as shown in Table C20. The MMRM analysis permits testing treatment effects at specific timepoints, which is more powerful than a two sample *t*-test and can take account of missing data in an unbiased fashion.[139]

[redacted], supporting conclusions of the significant benefits of selumetinib for patient HRQoL.[34]

Table C20. Change from baseline PedsQL patient- and parent-reported outcomes total score (MMRM)

PedsQL total score	Selumetinib, n									
	Self-reported (n=34b)					Parent-reported (n=50c)				
	Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle 13	Pre-Cycle 25	Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle 13	Pre-Cycle 25
Total responses	[redacted]									
Adjusted mean	[redacted]									
Standard error	[redacted]									
95% CI	[redacted]									
p-value[a]	[redacted]									

Footnotes: [a]Nominal p-value. [b]Children aged 8 to 18 years at enrolment expected to complete self-report measures of the PedsQL. [c]Parents or legal guardians of children aged 2 to 18 years at enrolment expected to complete the parent proxy measures of the PedsQL.
Abbreviations: CI: confidence interval; MMRM: mixed model repeated measures analysis.
Source: AstraZeneca Data on File (SRINT CSR).[34]

Impaired HRQoL was defined as total or domain scores falling one standard deviation (SD) below the population sample mean, as per the original approach defined by Varni et al. (2003) for the meaningful interpretation of PedsQL scores.[40, 140] Based on self-reported PedsQL total scores, [redacted]%) patients had impaired HRQoL at baseline. At pre-Cycle 13, [redacted] had impaired HRQoL, and [redacted] of patients showed a clinically meaningful improvement in HRQoL above the CMT. These results were maintained through to pre-Cycle 25, where [redacted] had impaired HRQoL, and [redacted] of patients showed a clinically meaningful improvement in HRQoL above the CMT.[34] Based on parent-reported PedsQL total scores, [redacted] patients had impaired HRQoL at baseline. At pre-Cycle 13, [redacted] with parent-reported scores had impaired HRQoL, and [redacted] patients showed an improvement in HRQoL based on the CMT. These results were maintained through to pre-Cycle 25, where only [redacted] had impaired HRQoL and [redacted] patients showed a clinically meaningful improvement in HRQoL above the CMT.[34]

The parent-reported scores showed a greater percentage of patients with impaired HRQoL at baseline, and a greater clinically meaningful improvement in patient HRQoL than self-reported scores. However, a substantial proportion of both patients and parents reported [redacted] indicating a sustained benefit of treatment with selumetinib on patients' HRQoL as perceived by patients as well as their parents.[34]

PN-associated pain

Pain is a key driver of disease burden for patients with NF1 PN and can have severe impacts on patients' HRQoL and daily functioning (see Section 7.1). In SPRINT Phase II Stratum I, selumetinib-treated patients and their parents reported clinically meaningful improvements in pain intensity and pain interference with daily functioning, again demonstrating the life-changing clinical benefits of selumetinib.

The Numerical Rating Scale 11 (NRS-11) was used to assess pain intensity; patients aged 8 to 18 years at enrolment completed self-report measures of NRS-11. Improvements in PN-related pain intensity for self-selected and target PN pain, overall PN pain and other pain, demonstrated by a decrease in pain intensity scores from baseline, [redacted] (Figure C10). [34]

Figure C10. Mean change from baseline of NRS-11 pain intensity scores in SPRINT Phase II Stratum I

Footnotes: [a]Patients who had their baseline evaluation using an earlier version of the NRS-11, which did not yet include the target tumour item, were considered only if self-selected and target PN were the same.
Abbreviations: CI: confidence interval; NRS-11; numerical rating scale 11.
Source: AstraZeneca Data on File (SPRINT CSR)[34]

In total, [redacted] patients completed NRS-11 assessments for physician-selected target PN pain at baseline and at the pre-Cycle 13 visit. At baseline, the median score for target PN pain intensity was [redacted] compared to [redacted] at pre-Cycle 13 [redacted], showing [redacted]. At pre-Cycle 13, [redacted] showed a decrease of at least 2 points in the score, considered a clinically meaningful improvement. Of these [redacted], [redacted] who showed no change in PN-related pain intensity had a pain score of 0 or 1 at baseline and therefore could not improve their score by two points or more. [redacted].[34]

A decrease from baseline in target PN pain intensity scores was also seen [redacted] based on MMRM analysis (Figure C11). At pre-Cycle 13, the adjusted mean change from baseline in physician-selected target PN pain was [redacted] considered clinically meaningful; [redacted].[34]

Figure C11. Adjusted mean change from baseline of NRS-11 target tumour pain score, MMRM in SPRINT Phase II Stratum I

Abbreviations: CI: confidence intervals; MMRM: mixed model repeated measures; NRS-11: numerical rating scale 11.
Source: AstraZeneca Data on File (SPRINT CSR)[34]

Associations between post-baseline longitudinal changes in NRS-11 and changes in PN volumes were also assessed. MMRM analysis suggested [redacted].[34] When results from the NRS-11 were compared to data collected on pain medication use, it was found that [redacted] with a baseline NRS-11 score of at least 2 points had a reduction in pain intensity without increased analgesic use during selumetinib treatment. Pain palliation occurred within [redacted], with the median time to pain palliation being reached [redacted].[34]

The PII index was used to assess pain interference with daily functioning. Overall, improvements from baseline in self-reported and parent-reported PII scores were [redacted] (Figure C12 and Figure C13). For the [redacted] who completed self-reported PII assessments at baseline and pre-Cycle 13, [redacted]. Of these [redacted] showed a clinically meaningful improvement and one patient showed deterioration at pre-Cycle 13. For the [redacted] who had parent-reported PII assessments at baseline at pre-Cycle 13, [redacted]. Of these [redacted] showed a clinically meaningful improvement and [redacted] at pre-Cycle 13.[34]

Figure C12. Adjusted mean change from baseline for PII self-report pain interference total score, MMRM in SPRINT Phase II Stratum I

Abbreviations: CI: confidence interval; MMRM: mixed model repeated measures; PII: pain interference index.
Source: AstraZeneca Data on File (SPRINT CSR)[34]

Figure C13. Adjusted mean change from baseline for PII parent-report pain interference total score, MMRM in SPRINT Phase II Stratum I

Abbreviations: CI: confidence interval; MMRM: mixed model repeated measures; PII: pain interference index.
Source: AstraZeneca Data on File (SPRINT CSR)[34]

Results of the NRS-11 and PII demonstrate the capacity of selumetinib to have a positive, clinically meaningful impact on PN-associated pain, [redacted]. These decreases in PN-associated pain are likely to contribute to the improvements in HRQoL demonstrated in SPRINT Phase II Stratum I (see Section 9.6.1). In addition, patients in SPRINT Phase II Stratum I [redacted], in contrast to patients enrolled on the Natural History study for whom pain medication use increased over time (see Section 6.1), again demonstrating the positive impact of selumetinib.

Motor function

Physical functioning and physical activity were assessed through the PROMIS mobility and upper extremity scales.

There was a trend towards [redacted] as reported by both parents and patients.[34] Between baseline and pre-Cycle 13, [redacted]. The mean T-scores also showed [redacted].[34]

Manual muscle testing (MMT) demonstrated [redacted]. At baseline, the median muscle strength score in the affected body quadrant was [redacted]. When scores were adjusted for age, [redacted]. In the MMRM analysis of the of strength MMT [redacted] (Figure C14). Improvement in strength [redacted].[34]

Figure C14. Adjusted mean change from baseline of strength measured by the manual muscle test, MMRM

Abbreviations: CI: confidence interval; MMRM: mixed model repeated measures; PII: pain interference index.
Source: AstraZeneca Data on File (SPRINT CSR)[34]

In an MMRM analysis of patients with a target PN in any body quadrant, [redacted].[34]

Overall, these results demonstrate improvements in mobility, upper extremity scores, range of motion and strength, in particular for PN-related body quadrants, for patients treated with selumetinib, as perceived by the patients themselves as well as their parents. This is in contrast to the Natural History study where growth of PN over time was observed to lead to increasing severity of motor dysfunction.[11]

Airway function

Of the 11 patients with airway morbidity and without tracheostomy at baseline, median forced expiratory volume in one section (FEV_1) [redacted]. This trend in improvement was [redacted]. Of the [redacted] assessed for FEV_1, [redacted] showed no change in FEV_1, whilst [redacted]. While R_{20} [redacted] No patients enrolled in this study had a baseline score on the Apnoea-Hypopnoea Index (AHI) of >5, considered to be the lower limit necessary to see a meaningful effect of treatment. The observed effect on FEV_1 scores indicates a benefit for patients treated with selumetinib in maintaining airway function and thus avoiding more severe morbidities associated with the growth of PN near airways.

Bowel and bladder function

Due to insufficient responses at baseline ([redacted]), it was not possible to assess self-reported outcomes of bowel and bladder function using the dysfunctional voiding questionnaire (DVQ). [redacted].[34]

Visual function

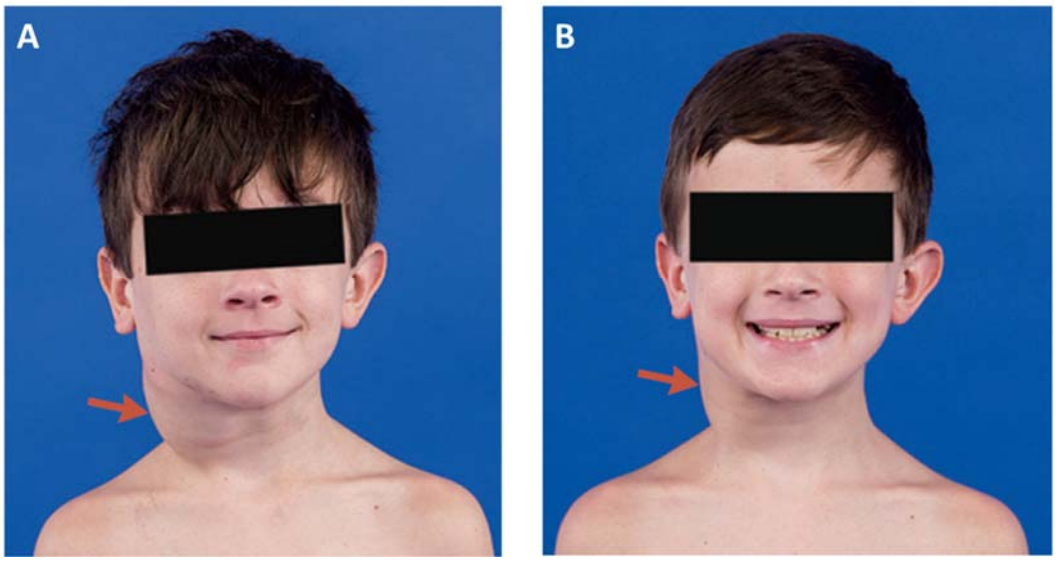
Baseline and pre-Cycle 13 assessments for visual acuity were reported for [redacted]. Mean visual acuity trended [redacted], but these changes may be impacted by the small number of patients and variability due to patient age. Mean visual acuity [redacted].[34]

There was wide variability in measurements for exophthalmometry at each time point, particularly at pre-Cycle 13. Of the seven patients evaluated at pre-Cycle 13, [redacted].[34] There is a wide range of normal distribution for exophthalmometric measurements, which further vary based on age and ethnicity; this may have contributed to the variability over time.[141]

Disfigurement

Improvements in disfigurement in PN from baseline in a range of locations, including the head and neck, trunk and extremities of the body were seen with selumetinib treatment (Figure C15).[18, 34] With disfiguring facial PN in particular having been shown to have a negative impact on patients' social/physical functioning and self-esteem,[13, 26] it can be expected that this effect of treatment with selumetinib would result in a wide-reaching benefit on patients' lives.

Figure C15. Change in PN-associated disfigurement following selumetinib treatment



Footnotes: A: patient at baseline. B: patient at pre-Cycle 13 (following 12 Cycles of selumetinib treatment). Arrow indicates the disfiguring PN.
Abbreviations: PN: plexiform neurofibroma.
Source: Gross et al. 2020.[18]

Secondary outcome: global impression of change

Results from the SPRINT CSR are presented within this section.

In SPRINT Phase II Stratum I, GIC was used to evaluate the clinical significance of changes in PN-associated morbidities, which is valuable in this setting due to the heterogeneity of symptoms between patients.[34] Use of patient- and parent-reported GIC enables a broader understanding of the impact of selumetinib on disease burden, than with the other functional assessments and PRO tools previously discussed.[34]

At pre-Cycle 13, [redacted] patients and [redacted] parents reported some level of improvement with respect to the child's tumour-related morbidity (Figure C16). Only [redacted] reported changes as being "minimally worse". [redacted] reported changes as being "much worse" or "very much worse", indicating an overall positive trend in the perception of PN-related morbidity over time as a result of treatment with selumetinib.

Figure C16. Distribution of GIC self- and parent-reported PN-related morbidity over time

Footnotes: [a]Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the GIC. [b]Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC. Percentages were based on the number of patients with a non-missing score at each analysis visit.
Abbreviations: GIC: global impression of change; PN: plexiform neurofibromas.
Source: AstraZeneca Data on File (SRINT CSR).[34]

Morbidity-specific improvements

For both self-reported and parent-reported GIC, [redacted] (summarised in Figure C17 and Figure C18 respectively). [redacted].[34] Overall, these results suggest a consistently positive impact of treatment with selumetinib on patients' experience of pain over time.

Figure C17. Distribution of GIC self- and parent-reported PN-related pain over time

Footnotes: [a]Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the GIC. [b]Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC. Percentages were based on the number of patients with a non-missing score at each analysis visit.
Abbreviations: GIC: global impression of change.
Source: AstraZeneca Data on File (SRINT CSR).[34]

Figure C18. Distribution of GIC self- and parent-reported overall pain over time

Footnotes: [a]Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the GIC. [b]Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC. Percentages were based on the number of patients with a non-missing score at each analysis visit.
Abbreviations: GIC: global impression of change.
Source: AstraZeneca Data on File (SRINT CSR).[34]

In addition, during the completion of the GIC questionnaire, patients were able to describe the changes they had noticed in their PN and associated morbidities; given the diverse nature of the disease, and accordingly the diversity of benefits from selumetinib treatment, a selection of quotes from patients has been presented in Table C21. These anecdotal improvements highlight how selumetinib facilitates a more normal life for patients, with improvements in physical function and reduced pain frequently noted. Many patients and their parents reported an improvement in their appearance, with [redacted] describing improved appearance after one year of treatment.[34]

Table C21. Quotes from GIC questionnaire for selected patients

Patient PN morbidity assignment(s)a	Patient quote (timepoint)	Parent/carer quote (timepoint)
Airway, disfigurement	[redacted]	[redacted]
Airway, disfigurement	[redacted]	[redacted]
Disfigurement	[redacted]	[redacted]
Disfigurement, pain, vision	[redacted]	[redacted]
Disfigurement, motor, pain	[redacted]	[redacted]
Bowel/bladder, disfigurement, motor, pain	[redacted]	[redacted]

Footnote: [a]Quotes within the same table row represent an individual patient enrolled within the SPRINT Phase II Stratum I. [b]Patient was too young to be eligible for GIC self-report.
Abbreviations: GIC: global impression of change; PN: plexiform neurofibromas.
Source: AstraZeneca Data on File (Individual Patient Reviews).[93]

9.6.2 Justify the inclusion of outcomes from any analyses other than intention-to-treat.

Not applicable.

9.7 Adverse events

Summary of Section 9.7

- The safety profile of selumetinib, evaluated in SPRINT Phase II Stratum I, is consistent with previous trials of the drug in adult and paediatric populations[39, 58]
- Overall, the safety results indicate that selumetinib has a predictable and manageable safety profile, and would therefore be suitable for long-term treatment in children with symptomatic, inoperable NF1 PN:[34, 39, 58]
    - Overall, [redacted] of patients experienced AEs and [redacted] of patients experienced Grade ≥3 AEs. [redacted]
    - The most common AEs of any grade were [redacted]
    - The most common Grade ≥3 AEs were [redacted]
    - Serious AEs (SAEs) observed included [redacted]. All SAEs with known outcomes [redacted]
    - AEs of special interest (AESI) were [redacted], with [redacted] of patients experiencing an AESI of Grade ≥3. AESIs were generally resolved with dose modification and/or with supportive therapy
    - AEs could generally be managed using dose interruptions (occurring in [redacted] of patients) and dose reductions (occurring in [redacted] patients), rather than treatment discontinuation ([redacted] of patients)
    - Dose interruptions had a minimal impact on treatment exposure; the total treatment duration ([redacted]) did not differ significantly from the actual treatment duration ([redacted])

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse event data were identified using the search strategy for clinical evidence from published and unpublished trials, as described in Section 9.1 and the Appendix (Section 17.3).

9.7.2 Provide details of all important adverse events reported for each study.

Safety and tolerability results reported here for SPRINT Phase II Stratum I are from the 90DSU (29th March 2019 DCO).[58] Where appropriate, additional details of AEs which took place during the period of the first DCO (29th June 2018) have been reported from the CSR.[34]

Study drug exposure

At the 90DSU, [redacted] were receiving selumetinib treatment. The difference between the median total and median actual treatment duration was small [redacted], indicating that dose interruptions were generally short, did not impact exposure, and that selumetinib was well tolerated. The duration of exposure to selumetinib is summarised in Table C22.[58]

Table C22. Exposure to selumetinib

AEs	Selumetinib (N=50)
Total treatment duration, days[a]	
Mean (SD)	[redacted]
Median (min–max)	[redacted]
Total treatment years	[redacted]
Total treatment duration[b]	
<12 months, n (%)	[redacted]
≥12 to ≤24 months, n (%)	[redacted]
>24 to ≤36 months, n (%)	[redacted]
>36 to ≤48 months, n (%)	[redacted]
>48 months, n (%)	[redacted]
Actual treatment duration, (days)[c]	
Mean (SD)	[redacted]
Median (min–max)	[redacted]
Total treatment years	[redacted]

Footnotes: [a]Total treatment duration = (last dose date – first dose date + 1). For re-treatment patients, this excludes the off-treatment period between treatment discontinuation and re-treatment. [b]One month = 30.4375 days. [c]Actual treatment duration = sum of days of study dose administered.
Abbreviations: AE: adverse event; SAE: serious adverse event; SD: standard deviation.
Source: AstraZeneca Data on File (90 day safety update).[58]

Summary of AEs

A summary of AEs in SPRINT Phase II Stratum I is presented in Table C23.[93] The relative risk and risk difference and associated 95% confidence intervals for each AE were not calculated in SPRINT Phase II Stratum I.

Although the majority of patients in the trial reported AEs ([redacted]), they were mostly non-serious. Only [redacted] experienced SAEs and [redacted] experienced treatment-emergent SAEs. [redacted]. AEs could generally be managed using dose interruptions, symptomatic or supportive care, and subsequently resolved; [redacted] experienced dose interruptions due to AEs and [redacted] discontinued due to AEs. Consistent with previous safety assessments for selumetinib, no irreversible or cumulative toxic effects were noted.

The long-term safety of selumetinib continues to be assessed in the SPRINT trial.[58]

Table C23. Summary of adverse events

AEs	Selumetinib (N=50)
All grade AEs, n (%)	[redacted]
Grade ≥3 AEs, n (%)	[redacted]
Treatment-emergent grade ≥3 AEs, n (%)	[redacted]
SAEs, n (%)	[redacted]
Treatment-emergent SAEs[a], n (%)	[redacted]
Deaths, n (%)	[redacted]
Dose interruptions due to AEs, n (%)	[redacted]
Dose reductions due to AEs, n (%)	[redacted]
Discontinuations due to AEs, n (%)	[redacted]

Footnotes: [a]As assessed by the investigator and including possibly, probably or definitely related to selumetinib treatment.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: AstraZeneca Data on File (90 day safety update).[58]

Common AEs

A summary of the most common AEs (≥50% of patients) experienced in SPRINT Phase II Stratum I is presented in Table C24. The two most common AEs experienced were [redacted].[58]

Table C24. Common AEs (>50%)

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Vomiting	[redacted]
Blood creatine phosphatase increased	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]

Dry skin	[redacted]
Pyrexia	[redacted]
Fatigue	[redacted]
Dermatitis acneiform	[redacted]
Hypoalbuminaemia	[redacted]
Headache	[redacted]
Oropharyngeal pain	[redacted]
Stomatitis	[redacted]

Footnotes: Table is sorted by frequency for preferred terms at DCO for 90DSU and includes events experienced by ≥50% of patients. Patients with multiple events in the same PT are only counted once in that PT. Patients with events in more than one PT were counted once in each of those PTs. Includes AEs with and onset date on or after the first dose and up to and including 30 days following the last dose of selumetinib. MedDRA version 21.0.
Abbreviations: 90DSU: 90 day safety update; AE: adverse event; DCO: data cut-off; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.
Source: AstraZeneca Data on File (90 day safety update).[58]

Grade ≥3 AEs

Grade ≥3 AEs were reported in [redacted] of selumetinib-treated patients (Table C25).[58] AEs of Grade ≥3 were most commonly reported [redacted]. By preferred term (PT), the most commonly reported AEs of Grade ≥3 were [redacted]

Table C25. AEs for CTCAE Grade ≥3

SOC/MedDRA preferred term	Selumetinib (N=50), n (%)[a]
Patients with AE CTCAE Grade ≥3, n (%)	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Vomiting	[redacted]
Dental caries	[redacted]
Nausea	[redacted]
Investigations	[redacted]
Weight increased	[redacted]
Blood creatine phosphokinase increased	[redacted]
Alanine aminotransferase increased	[redacted]
Lipase increased	[redacted]
Infections and infestations	[redacted]
Paronychia	[redacted]
Skin and subcutaneous tissue disorder	[redacted]

Dermatitis acneiform	[redacted]
Eczema	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Reparatory, thoracic and mediastinal disorders	[redacted]
Hypoxia	[redacted]
Nervous system disorders	[redacted]
Syncope	[redacted]
Blood and lymphatic system disorders	[redacted]
Anaemia	[redacted]

Footnotes: Table includes AEs of Grade ≥3 which were reported in ≥2 patients, with an onset date on or after the date of first dose and up to and including 30 days following the last dose of selumetinib. MedDRA version 21.0, CTCAE version 4.0. [a]Each patient has only been represented with the maximum reported CTCAE grade for each system organ class/preferred term.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class.
Source: AstraZeneca Data on File (90 day safety update).[58]

Serious AEs

SAEs, classified as important medical events, were reported in [redacted] selumetinib-treated patients (Table C26).[58] [redacted] SAEs were known adverse drug reactions (ADRs, AEs which have been identified as causally related to selumetinib) for selumetinib ([redacted]).

Table C26. Summary of SAEs related to selumetinib treatment reported in ≥2 patients

System organ class and preferred term	Selumetinib (N=50), n (%)
Patients with any SAE	[redacted]
Patients with any SAE causally related to treatment[a]	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Blood and lymphatic system disorders	[redacted]
Anaemia	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Hypoxia	[redacted]

Footnotes: Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of selumetinib. [a]As assessed by the investigator and including possibly, probably or definitely related to selumetinib treatment.
Abbreviations: SAE: serious adverse event.
Source: AstraZeneca Data on File (90 day safety update).[58]

[redacted] experienced MPNST as an SAE, involving the malignant transformation of a PN; none were considered to be related to selumetinib treatment.[34, 58] [redacted]

[redacted]

At DCO (March 29th 2019, 90DSU), except for [redacted], all SAEs had resolved with either no action taken, following a dose interruption or delay/dose reduction, or following selumetinib discontinuation.[34, 58]

AEs of special interest

Prior to database lock, certain medical concepts and PTs were defined as being AESIs, based on the established effects of MEK inhibition, non-clinical findings and emerging data from ongoing clinical studies with selumetinib.[58] Table C27 summarises AESIs, which were experienced by [redacted] Overall, AESIs were [redacted], and generally resolved whilst on selumetinib treatment, with dose modification and/or with supportive therapy.[58]

Table C27. AEs of special interest for selumetinib

AEs	Selumetinib (N=50), n (%)
Patients with any AESI	[redacted]
Grade ≥3	[redacted]
Erythropaenic effects[a]	[redacted]
Grade ≥3	[redacted]
Leukopaenic effects[b]	[redacted]
Grade ≥3	[redacted]
Thrombocytopaenic effects[c]	[redacted]
Grade ≥3	[redacted]
Cardiac events[d]	[redacted]
Grade ≥3	[redacted]
Muscular events[e]	[redacted]
Grade ≥3	[redacted]
Physeal dysplasia	[redacted]
Grade ≥3	[redacted]
Nail disorders[f]	[redacted]
Grade ≥3	[redacted]
Oral mucositis effects[g]	[redacted]
Grade ≥3	[redacted]
Rash acneiform[h]	[redacted]
Grade ≥3	[redacted]
Rash non-acneiform[i]	[redacted]
Grade ≥3	[redacted]
Retinal events[j]	[redacted]
Grade ≥3	[redacted]

Footnotes: PTs reported: [a]Anaemia. [b]Lymphocyte count decreased, neutrophil count decreased, white blood cell count decreased. [c]Platelet count decreased. [d] Ejection fraction decreased, oedema peripheral, peripheral swelling, right ventricular ejection fraction decreased. [e]Acute kidney injury, blood creatine phosphokinase increased, blood creatinine increased, hypocalcaemia, muscular weakness, musculoskeletal pain, myalgia. [f]Paronychia. [g]Mouth ulceration, stomatitis. [h]Dermatitis acneiform. [i]Pruritus, rash, rash erythematous, rash maculo-papular, rash pruritic. [j]Chorioretinal scar, photophobia, vision blurred, vitreous disorder.
Abbreviations: AE: adverse events; AESI: adverse events of special interest; PT: preferred term.
Source: AstraZeneca Data on File (90 day safety update).[58]

Dose interruptions, reductions and continuations

Dose interruptions

Whilst dose interruptions occurred in [redacted], single missed doses were counted as dose interruptions, contributing to the relatively high number of interruptions recorded.[58] The most common reasons for dose interruptions were '[redacted] [58] Dose interruptions of selumetinib due to AEs occurred in [redacted]. The most common AEs (reported in >5 patients) that resulted in treatment interruption were [redacted] the majority of which are ADRs for selumetinib.[58]

Dose reductions

In total, [redacted] had dose reductions due to AEs; the majority of AEs that were causally attributed to selumetinib and led to dose reduction were Grade ≥3.[58] All of the AEs which required a dose reduction resolved and were managed with symptomatic and/or supportive treatment where necessary. The selumetinib ADRs which lead to dose reductions included [redacted].[58]

Discontinuation

Discontinuation of selumetinib due to AEs occurred in [redacted]. [redacted] resolved after selumetinib was stopped; [redacted] at DCO (29th Mar 2019, 90DSU). The most common system organ class AEs leading to permanent discontinuations was [redacted] [58]

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

The safety of selumetinib in paediatric patients was evaluated in the SPRINT Phase I/II clinical trial. Phase I of the SPRINT trial, which enrolled paediatric NF1 patients with inoperable PN, demonstrated that selumetinib had acceptable rates of dose-limiting toxic effects when administered over a long-term basis (median treatment duration 75.5 cycles), with skin and gastrointestinal toxic effects being the most common AEs.[39, 66] These results are consistent with those observed in SPRINT Phase II Stratum I, which enrolled patients with symptomatic, inoperable NF1 PN. The safety analysis population is therefore directly aligned with the scope of this submission.

Results of SPRINT Phase II Stratum I indicate that selumetinib has a generally predictable and manageable safety profile in paediatric patients with NF1 PN, and would be suitable for long-term treatment. The majority of AEs were mild or moderate in severity, with the most common AEs being vomiting [redacted] and increased blood creatine phosphokinase

[redacted]. AEs could generally be managed using dose interruptions [redacted] and dose reductions [redacted], rather than treatment discontinuation [redacted]. Overall, dose interruptions had a minimal impact on treatment exposure; the total mean treatment duration [redacted] did not differ significantly from the actual mean treatment duration [redacted].[58]

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Propensity score analyses

Although the naïve comparison between the SPRINT Phase II Stratum I and Natural History studies were justified due to the methodological overlap (Section 9.4.1 to 9.4.3), propensity score analyses were explored to understand the potential impact of adjusting for baseline covariates across the study populations on estimates of treatment effect.

- As the SPRINT Phase II trial is a single arm study, in the absence of a control arm, naïve comparisons to external controls were performed to determine the comparative effectiveness of selumetinib versus established clinical management (as described in Section 9.4.1). However, naïve comparisons may potentially lead to biased estimates of treatment effects if there are differences across trials that could have an impact on the results, such as differences in baseline patient characteristics. [142, 143]

- Propensity score matching is a well-documented approach for reducing this risk of bias.[144] The propensity score is defined as the probability of being treated, conditional on observed baseline characteristics (covariates).[145] This score can be used to balance the covariates between two groups, reducing bias in comparisons accordingly.[142, 143]

In the estimation of treatment effects, propensity score analysis was performed for the comparison of PFS between selumetinib-treated patients from SPRINT Phase II Stratum I vs patients treated with established clinical management only from the Natural History study.[142, 143] The analyses were conducted in line with the recommended approach detailed in NICE DSU TSD18, as detailed below.[144]

Four different methods were performed to investigate the risk of bias for the comparison of the SPRINT Phase II Stratum I and Natural History study populations:

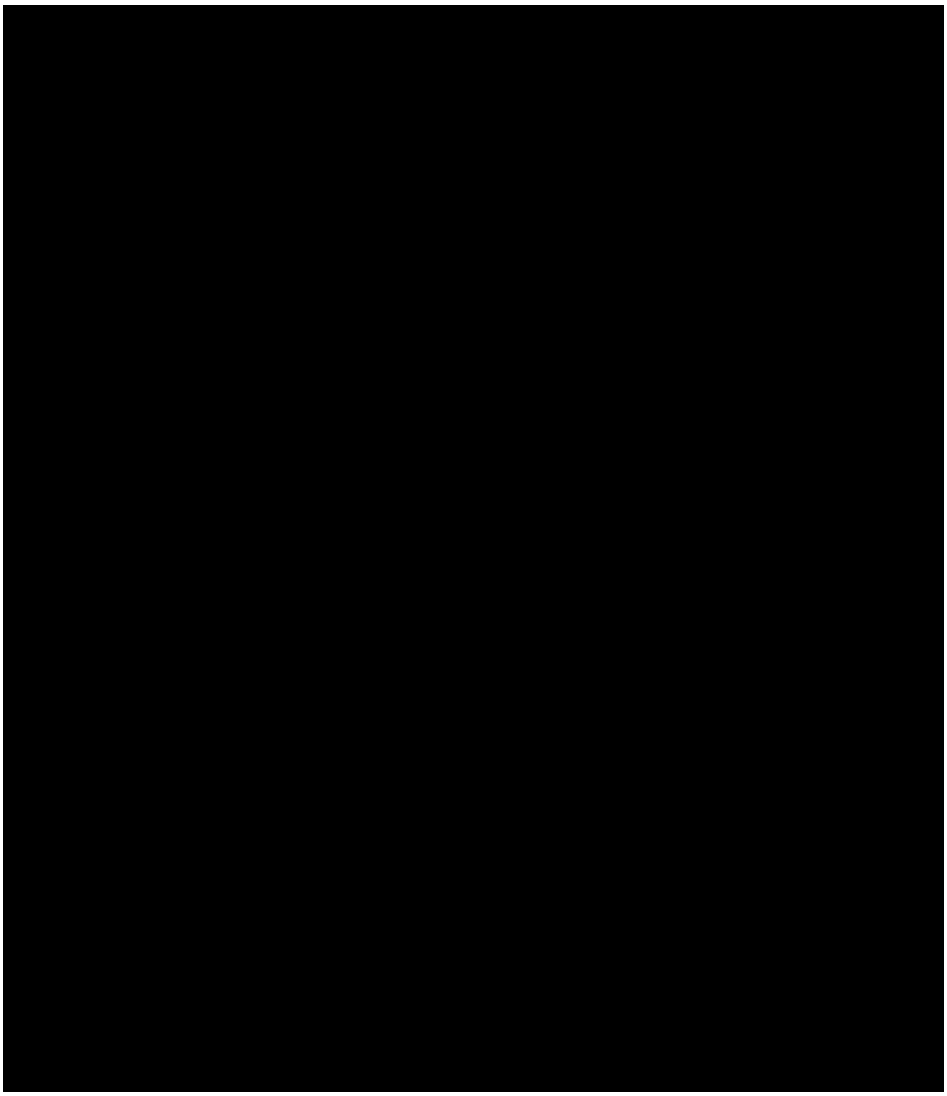
1. Matched 1:1 (without replacement) with a robust variance
2. Weighted using stabilised Inverse Probability of Treatment Weighting (IPTW)
3. Weighted using IPTW, with a robust variance
4. Matched 1:2 (with replacement) with a robust variance

As these analyses were performed by AZ, they were based on the PFS data reported in the SPRINT CSR (DCO 29th June 2018), rather than that in the Gross et al. (2020) publication (see Section 9.4.2).

Patient eligibility

Data were complete for all 50 patients in SPRINT Phase II Stratum I, therefore, all patients were considered in the analysis. A small number of patients who were included in the Natural History age-matched cohort were subsequently enrolled in SPRINT ([redacted]). In order to maintain independency between the two studies, data for these [redacted] patients were excluded for the Natural History arm of this comparison. Patients with missing weight and height at first MRI assessment of target PN ([redacted]) were also excluded. [redacted] patients from the Natural History study were ultimately eligible for propensity score analysis. A flow chart demonstrating patient eligibility is presented in Figure C19.

Figure C19. Propensity score analysis patient eligibility



Abbreviations: MRI: magnetic resonance imaging; NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.

Propensity score matching 1:1 (without replacement)

The propensity score for selumetinib treatment was estimated using multivariate logistic regression, where:

- The study (SPRINT Phase II Stratum I for selumetinib treatment, Natural History for established clinical management) was fitted as the dependent variable
- All baseline covariates (age, race, gender, weight, height, PN volume and target PN location) were fitted as independent variables, in line with recommendations from the Committee for Medicinal Products for Human Use (CHMP)[146]
- Age, weight, height and target PN volume were kept as continuous variables

For the 1:1 matching, each SPRINT patient was calliper-matched by propensity score to one eligible Natural History patient using a greedy matching algorithm. A calliper width of 0.2 of the pooled SD of the logit of the propensity score was used. In total, [redacted] from the SPRINT study were matched to [redacted] patients from the Natural History study using the propensity scores.

Inverse probability of treatment weighting

Each patient from the SPRINT Phase II Stratum I (selumetinib-treated) and eligible Natural History study (established clinical management) was assigned a weight based on the inverse of the propensity score. Stabilised weights were used in order to preserve the sample size of the original data, to produce an appropriate estimation of the variance of the main effect and to maintain an appropriate type I error rate. As there were no extreme weights, no further adjustment to the weights such as capping was required. All weights were below 3 for SPRINT and below for the Natural History study, respectively.

Propensity score matching 1:2 (with replacement)

Increasing the matching ratio above 1:1 is thought to generally improve precision (and decrease confidence intervals), but may also increase bias, as second matches will generally be of lower quality than first matches.[147]

As a sensitivity analysis, each patient from the SPRINT Phase II Stratum I was matched to up to two eligible patients from the Natural History study using the propensity scores. Matches were found for [redacted] from SPRINT Phase II Stratum I, with replacement (i.e. eligible patients from the Natural History study could have been used multiple times). These matches were based on [redacted] from the Natural History study. Weighting was conducted in accordance with the method proposed by Ho *et al.* (2011) and used to weight patients in order to get a sum of the weights equal to the total number of unique patients used in the matched analysis.[148]

Comparison of baseline characteristics before and after matching

The baseline characteristics for all eligible patients pre-matching/weighting, and after each method of propensity score matching/weighting (1:1 matching, stabilised IPTW and 1:2 matching) are presented in Table C28.

Baseline characteristics were compared between eligible SPRINT Phase II Stratum I and Natural History study patients, by calculating standardised difference, defined as the absolute difference

in sample means (for continuous variables) or proportions (for binary variables) over the pooled SD of the variable. Before matching/weighting, the eligible SPRINT Phase II Stratum I and the Natural History study populations [redacted]. In contrast, the eligible Natural History study population [redacted], whilst SPRINT Phase II Stratum I had [redacted]. Patients in SPRINT Phase II Stratum I were [redacted].

After matching/weighting, baseline characteristics were [redacted][149]. However, the matched analyses did also result in a reduction in the sample sizes.

Table C28. Baseline characteristics for all patients included in the propensity score analysis before matching/weighting, and after propensity score matching/weighting

		Pre-matching/weighting			1:1 matching			Stabilised IPTW			1:2 matching		
Variable		SPRINT ([redacted])	NH ([redacted])	Std. Diff.	SPRINT ([redacted])	NH ([redacted])	Std. Diff.	SPRINT ([redacted])	NH ([redacted])	Std. Diff.	SPRINT ([redacted])	NH ([redacted])	Std. Diff.
Sex n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Race n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Age (years)	Mean, SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	Mean, SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height (cm)	Mean, SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Target PN volume (L)	Mean, SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Target PN	Head/Neck/ Trunk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Pre-matching/weighting			1:1 matching			Stabilised IPTW			1:2 matching		
Variable		**SPRINT ([redacted])**	**NH ([redacted])**	**Std. Diff.**	**SPRINT ([redacted])**	**NH ([redacted])**	**Std. Diff.**	**SPRINT ([redacted])**	**NH ([redacted])**	**Std. Diff.**	**SPRINT ([redacted])**	**NH ([redacted])**	**Std. Diff.**
location n (%)	Trunk/Extremity / Whole Body	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	

Abbreviations: IPTW: inverse probability of treatment weighting; N: number of patients included in analysis; NH: Natural History Study; PN: plexiform neurofibromas; SD: standard deviation; Std. Diff: absolute standardised difference.

Results

The results of **the propensity score matching analyses confirm that selumetinib strongly reduces the risk of progression**, in comparison to established clinical management (Table C29).. The **results were highly consistent across all four additional analyses, demonstrating a high degree of robustness to the choice of method used for comparison**.

Kaplan-Meier curves for the analyses (naïve, weighted, matched 1:1 without replacement, and matched 1:2 with replacement) are presented in the Appendix (Section 17.7.2).

Table C29. HR for PFS for the naïve comparison and for the propensity score analyses

Analysis	Hazard Ratio[d]	95% CI	p-value
Cox model: Naïve comparison	[redacted]	[redacted]	[redacted]
Cox model: Matched patients 1:1 (robust variance estimator)[a,b]	[redacted]	[redacted]	[redacted]
Cox model: Weighted by stabilised IPTW	[redacted]	[redacted]	[redacted]
Cox model: Weighted by IPTW (robust variance estimator)	[redacted]	[redacted]	[redacted]
Cox model: Matched patients 1:2 (robust variance estimator)[b,c]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Greedy Matching algorithm is used without replacement. [b]The difference in the logit of the propensity score for a match must be ≤0.2 times the pooled estimate of the common standard deviation of the logits of the propensity scores. [c]Each treated patient is matched up to 2 controls. Matching is performed with replacement. dHRs were obtained using Cox regression with study as the only covariate.
Abbreviations: CI: Confidence interval; IPTW: inverse probability of treatment weighting; HR: hazard ratio; NH: Natural History; PFS: Progression-free survival.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

NF1 PN is a rare, complex, lifelong, incurable, progressive, genetic disease in which symptoms arise in childhood and continue into adulthood. Associated morbidities such as pain, disfigurement and motor dysfunction lead to reduced HRQoL. In paediatric patients, PN display uncontrolled and unpredictable growth over time, and this growth is associated with increasing number and severity of morbidities.[11] Treatment options for NF1 PN are extremely limited; though surgery can be used to reduce PN volume, it is associated with a high risk of complications[9, 12, 31] and many PN cannot be completely resected.[32] As a result, patients with symptomatic, inoperable NF1 PN have substantial unmet need.

Selumetinib treatment can reduce tumour volume and reduce/stabilise PN growth

Data from Stratum I of the SPRINT Phase II clinical trial demonstrated that **selumetinib treatment results in reductions in tumour volume, reduced or stabilised PN growth rates, extended PFS, and improvements in HRQoL for patients with symptomatic, inoperable NF1 PN**.[18] Selumetinib improved outcomes based on pre-planned comparative analyses against both the Natural History study and the placebo arm of tipifarnib Study 01-C-0222.[18, 34]

The primary outcome of the SPRINT Phase II Stratum I study was ORR, measured as the rate of cPR (≥20% decrease in PN volume from baseline) and CR to selumetinib.

- **The majority of NF1 PN patients receiving selumetinib in SPRINT Phase II Stratum I (68%) experienced a cPR to selumetinib treatment**, representing a ≥20% reduction in PN volume, confirmed across consecutive evaluations, from baseline. wherein contrast, no patients in the age-matched cohort of the Natural History study showed a reduction in PN volume of ≥20%.[18] These data demonstrate that **patients benefit from treatment with selumetinib through the reduction in volume of symptomatic PN**.[11, 18]

Secondary outcomes demonstrate that the response to selumetinib is durable. Of the 35 patients who had confirmed PR to selumetinib, 80% experienced a response that lasted for longer than one year. In total, 90% of all selumetinib-treated patients experienced a reduction in PN volume and 74% of patients had a BOR of ≥20% PN volume reduction. Finally, no patients receiving selumetinib experienced PN growth of ≥20% per year. In contrast to established clinical management alone, **selumetinib treatment results in *durable* reductions and stabilisation in tumour volume and PN growth in children with symptomatic, inoperable NF1 PN**.[18]

- **Children receiving selumetinib also show a much higher probability of PFS over three years, when compared to the age-matched Natural History cohort (84% vs**

15%, respectively).[18] An additional external comparison against the tipifarnib Study 01-C-0222 placebo arm,[41] and propensity score analyses of the Natural History cohort, support the conclusion that, **by inhibiting PN growth, selumetinib is superior to current established management options preventing disease progression and extending PFS in patients with NF1 PN**.

Selumetinib treatment can reduce PN-associated morbidity

Treatment with selumetinib can begin from as early as 3 years of age and continue as long as clinical benefit is observed, up until the age of 18. Initiating treatment with selumetinib in childhood, where the highest PN growth rates have been observed (see Section 6.1), can stabilise tumour volumes and prevent PN from reaching large volumes. Given that PN growth rate has been shown to plateau in adulthood, **selumetinib treatment is anticipated to limit the future lifetime impact of PN, including the number and severity of morbidities**. While long-term data on the use of selumetinib are not yet available, this benefit was supported by SPRINT:

- The majority of patients ([redacted]) reported some degree of improvement in [redacted] following selumetinib treatment. [redacted] at both pre-Cycle 13 and pre-Cycle 25.

- Meaningful improvements in HRQoL were reported by selumetinib-treated patients and their parents [redacted] over the first year of treatment; [redacted],[34] demonstrating that **the clinical improvements seen with selumetinib treatment have a positive impact on patients' everyday lives, through improved HRQoL and physical functioning**.[34]

Selumetinib is well-tolerated

Selumetinib was generally well tolerated in paediatric patients. The majority of AEs observed in SPRINT Phase II Stratum I were mild or moderate in severity.[34] Although [redacted] of patients experienced an AE of Grade ≥3 these could generally be managed using dose interruptions, symptomatic or supportive care. SAEs were reported in [redacted].[18, 34, 58]

Summary of clinical evidence

The data presented in this section from SPRINT Phase II Stratum I demonstrate that selumetinib can be expected to have important benefits for paediatric patients with symptomatic, inoperable NF1 PN through stabilisation/reduction in PN volume. These clinical benefits will be maintained into adulthood, reducing the substantial detrimental effects and HRQOL impact of NF1 PN that patients otherwise face for the remainder of their lives.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The strengths and limitations of any evidence base should be considered within the context of the disease. Several aspects of the design and features of the SPRINT study are a consequence of a clinical trial in a rare condition associated with heterogenous morbidity, and with no active comparator treatment available.

The population included within the SPRINT Phase II Stratum I, of paediatric NF1 patients aged ≥3 years with symptomatic, inoperable PN, is directly aligned with that stated in the decision problem and anticipated license for selumetinib.[34] Within the context of a rare condition, and, relative to the total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved a good sample size. Based on an assessment of baseline characteristics, patients from the SPRINT Phase II clinical trial are broadly representative of the UK paediatric NF1 PN patient population, despite being recruited from US sites, which has been confirmed by clinical experts in the UK (discussed further in Section 9.9.4).[28]

The SPRINT Phase II Stratum I trial provides evidence on a wide range of clinical and HRQoL outcomes of relevance to patients with NF1 PN. Tumour volumetric responses were evaluated using the REiNS criteria, which were developed by a committee of experts and have been used in a number of NF1 PN clinical trials.[18, 83, 84] These criteria are highly appropriate for evaluating PN responses to treatment. In addition, SPRINT Phase II Stratum I evaluated outcomes for a wide range of relevant PN-associated morbidities, including pain, physical functioning and HRQoL (see Section 6.1 for a full discussion of PN-associated morbidities).

The SPRINT Phase II Stratum I trial has investigated these outcomes over a long duration of follow-up, of three years for tumour volumetric data and safety outcomes; a longer follow-up is also planned.

To facilitate an assessment of selumetinib against current clinical management, pre-planned analyses using external control data from an age-matched cohort of patients enrolled in the Natural History study and the placebo arm of the tipifarnib Study 01-C-0222 were included as part of the protocol for SPRINT Phase II Stratum I.[34] This approach provides an analysis as close as possible to a controlled trial to assess the relative effectiveness of selumetinib. It was considered unethical to include a placebo arm directly in the SPRINT Phase II trial, given the significant disease morbidity faced by patients with inoperable, symptomatic NF1 PN, the absence of a disease-modifying treatment, and the results from Phase I of the SPRINT trial which demonstrated promising efficacy for selumetinib in this population.

The Natural History study is the largest study to date to examine the natural history and progression of NF1 PN under established clinical management; this study included a comprehensive and robust examination of PN growth and clinical outcomes. It was therefore the best possible external control arm available for comparison with the SPRINT Phase II Stratum I trial data. Since naïve comparisons generally cannot account for differences in baseline prognostic factors across studies, four different methods of propensity score matching were conducted to explore the comparability of the SPRINT and Natural History study populations (see Section 9.8.1). The results were robust to the choice of method and consistently demonstrated that selumetinib treatment strongly reduces the risk of progression compared with clinical management alone. Two limitations of the propensity score analyses are the resulting reduction in the effective sample size (from a SPRINT sample size of 50, to between 36−47, for the

different analyses [see Table C28]) and general issue of potential bias due to unobserved or unmeasurable confounding. Despite these limitations, the comparative assessments provide valuable evidence for the relative efficacy of selumetinib treatment compared with current clinical management using the best available data.[18, 34]

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base is aligned to the final scope, and is highly relevant, as outlined below.

Population

The SPRINT Phase II Stratum I population aligns well with the licensed indication, decision problem per the final scope, and with the UK patient population.

Comparator

In line with the final scope, the most relevant evidence is presented for the relative effectiveness of selumetinib versus current clinical management.

Pre-planned analyses using external control data from an age-matched cohort of patients enrolled in the Natural History study and the placebo arm of the tipifarnib Study 01-C-0222 were included as part of the protocol for SPRINT Phase II Stratum I. This approach provides an analysis as close as possible to a controlled trial to assess the relative effectiveness of selumetinib.

Outcomes

All outcomes listed in the submission scope have been provided. Additional outcomes of relevance to the scope were also presented, including duration of response, progression-free survival, time to progression, and global impression of change.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

As stated above, the limitations relating to study design and methodology coupled with the small number of patients are inevitable when undertaking a clinical trial of an active treatment for patients with a rare disease such as NF1 PN. No other factors are believed to influence the external validity of the SPRINT Phase II Stratum I results, on the basis of the following evidence.

Generalisability of study populations

The population investigated in Stratum I of the SPRINT Phase II trial is representative of patients seen in UK clinical practice, based on patient characteristics (see Section 9.4.3). As would be seen in the UK setting:[28]

- The trial population represents a wide range of baseline PN volumes, indicating that the results from the study are applicable to patients with varying levels of disease severity.
- Patients included in the trial also experienced a range of PN-associated morbidities prior at baseline, as would be seen in routine UK clinical practice and demonstrating the efficacy of selumetinib across the range of NF1 PN phenotypes found in the population.
- SPRINT Phase II Stratum I included patients from 3–18 years of age, with a median age of ten years, which is in line with the anticipated use of selumetinib in the UK based on clinical expert opinion.[18, 28, 34]

The pattern of prior and concurrent treatment in SPRINT Phase II Stratum I is anticipated to be broadly similar to that seen in patients in UK clinical practice, given the similarities between current treatment for NF1 PN in the US and UK.[18, 34] The lack of treatment options for NF1 PN internationally means that the disease is managed in a similar way in both the US (where the SPRINT trial was carried out) and the UK. Most patients in SPRINT Phase II Stratum I had received either a medical therapy or surgery, or both, prior to entering the SPRINT trial. In addition, patients continued to receive established clinical management, including pain medication, throughout the trial.

The populations of the comparator trials (Natural History study and tipifarnib Study 01-C-0222) are also expected to be representative of patients seen in UK clinical practice. The NCI Natural History study is a large observational study and provides a robust representation of real-world patient experiences. This further supports the validity of the using the Natural History study as an external comparator for SPRINT Phase II Stratum I.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

10 Measurement and valuation of health effects

Summary of Section C10

- **NF1 PN has a significant impact on the HRQoL of patients, negatively impacting several health domains including physical health, emotional wellbeing, and social development.** In many cases, the disease impairs patients' ability to live a normal life. There are currently no studies that describe HRQoL over the disease course of NF1 PN, and no dataset is available to depict the impact via utility values over patients' lifetimes for use in the cost-effectiveness analysis.
    - The SPRINT Phase II Stratum I trial assessed HRQoL as a secondary endpoint using the PedsQL 4.0 Generic Core Scales. PedsQL is a multi-dimensional measure of HRQoL that has been validated for use in children and adolescents and is highly appropriate for capturing patients' experiences on treatment with selumetinib.[43, 150]
    - The PedsQL measure however is not in line with the NICE reference case for cost-effectiveness analysis, where the preferred measure is the EQ-5D. There are no appropriate published, validated mapping algorithms for the PedsQL that are comparable enough to be applied to the patient population with NF1 PN. Furthermore, the SPRINT data are only available for patients treated with selumetinib, and for up to three years of follow-up, which means that even if utility values were to be generated, these would not be able to address the disease course of NF1 PN over the entire patient lifetime in the comparative analysis versus current clinical management. Therefore, alternative approaches to measuring HRQoL were required to conduct a robust analysis.
    - An SLR was conducted to identify published HRQoL data in patients with NF1, as well as their family and carers, however, no suitable utility data were identified.
- **To resolve the evidence gaps and to facilitate the economic evaluation of selumetinib versus current clinical management, a vignette-based time trade-off (TTO) study was conducted** by Acaster Lloyd Consulting, to estimate UK-specific utility values for patients with symptomatic, inoperable NF1 PN. Vignettes that appropriately and accurately reflected the disease course over a patient's lifetime were developed. The final vignette descriptions were based on a series of interviews with patients, parents/carers and clinical experts specialised in treating the target population, findings from the systematic and targeted literature reviews, and SPRINT Phase II Stratum I results.
    - The TTO study yielded utility values for two health states associated with symptomatic inoperable NF1 PN: [redacted] (patients without selumetinib) and [redacted] (patients with selumetinib)

- Selumetinib monotherapy has a generally predictable and manageable safety profile in paediatric patients with NF1 PN; AEs were usually mild or moderate in severity.[58] Such AEs experienced are likely to have a minimal impact on HRQoL.[28]

10.1 Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

NF1 PN is a rare and lifelong disease that has a significant impact on the HRQoL of patients, across all domains of health including **physical health, emotional wellbeing, and social development**. In many cases, the disease results in an **impaired ability to live a normal life** (Section 7.1).[25, 26] Through a range of morbidities, PN can affect multiple body regions and can reach large sizes, resulting in varied and often severe consequences:[8-11]

- **Physical functioning impairments** such as motor, airway, vision or bowel and bladder morbidities, can limit patient participation in physical activities and negatively impact social functioning[25, 26]
- The **burden of pain** can also limit physical activity, and greater pain interference is associated with **increased depression, anxiety, socialisation difficulties** and poorer overall QoL[19, 70]
- Patients express concerns around **PN-associated disfigurement** that is directly linked to body image and related stigma. This conveys that the condition not only impacts the way patients feel but how they are treated in society.[26] As a result, patients may have increased levels of depression, **withdrawal and attention problems, with associated educational and future employment detriments**[151]
- Children with NF1 PN experience unpredictable and uncontrolled PN growth and the clinical course of their disease is often unclear;[11, 18, 19] **the prospect of sudden disease progression which can ultimately lead to very large tumour volumes, worsened conditions and increasing morbidity has been identified as a key source of anxiety** for patients[25]

Further information on the burden of NF1 PN on patient HRQoL is presented in Section 7.1.

10.1.2 Please describe how a patient's health-related quality of life (HRQoL) is likely to change over the course of the condition.

As previously described, PN growth rates are most rapid in children with NF1 PN, with patients aged 3–5 years experiencing unpredictable and uncontrolled PN growth at a median growth rate of 35% per year.[11] These high growth rates can ultimately result in very large tumour volumes and an increased risk in both the number and severity of morbidities, with a substantial negative

impact on HRQoL.[11, 18, 19] As patients age, PN growth rates tend to slow and tumour volumes plateau into adulthood.[16, 17] Volume increases of ≥20% per year are rarely observed in adult patients,[16, 17] but patients will continue to experience the existing burden of PN-associated morbidities, resulting in poor HRQoL throughout their adult life with little hope of improvement.[11, 17, 19] Evidence for the continued lifelong HRQoL burden of NF1 PN is presented in Section 7.1.

10.2 HRQoL data derived from clinical trials

10.2.1 If HRQoL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQoL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQoL was assessed in SPRINT Phase II Stratum I as a secondary objective using the PedsQL 4.0 Generic Core Scales. PedsQL is a multi-dimensional measure of HRQoL that has been validated for use in children and adolescents and is appropriate for capturing patients' HRQoL on treatment with selumetinib.[43, 150, 43] Children from 8–18 years of age completed the PedsQL self-report version, and parents or legal guardians of children from 2–18 years of age completed the parent proxy version of the PedsQL.[43] PedsQL data were collected at baseline (prior to starting treatment), prior to cycles 3, 5, 9, 13, and then after every 12 cycles and at the end of therapy.

The results of the PedsQL are presented in Section 9.6 and show that [redacted]. A total of [redacted] of children and [redacted] of parents/carers reported [redacted] in PedsQL after one year of treatment. A clinically meaningful change was defined as greater than the minimal clinically important difference of 8.7 points for children and 8.1 points for parents/carers.[34]

10.3 Mapping

10.3.1 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

The PedsQL measure collected from the clinical trial is not in line with the NICE reference case for cost-effectiveness analysis, where the preferred measure is the EQ-5D. There are no appropriate published, validated mapping algorithms for the PedsQL that are comparable enough to be applied to the patient population with NF1 PN. Furthermore, the SPRINT PedsQL data are only available for patients treated with selumetinib, which means that even if any utility values were to be generated, these would not address the disease course of NF1 PN over the entire patient lifetime in the comparative analysis versus current clinical management. For these reasons, alternative approaches were considered necessary to conduct a robust analysis (see Section 10.4).

10.4 HRQoL studies

10.4.1 Please provide a systematic search of HRQoL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

An SLR was conducted to identify all literature published on HRQoL, cost and resource use, and economic evaluations in patients with NF1, as well as that of their families and carers. The SLR was performed between January and February 2021. Full details of the SLR search strategy and study selection process are reported in Section 11.1 and the Appendix (Section 17.4).

The number of records included and excluded at each SLR stage are presented in Figure D (Section 11.1). In total, ten publications reporting HRQoL data were identified, covering nine unique studies.

10.4.2 Provide details of the studies in which HRQoL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.

- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

Economic HRQoL SLR

A top-line summary of nine studies included in the economic SLR reporting HRQoL data can be found in Table C30, with full details of the studies summarised in the Appendix (Section 17.4.8).

The SLR yielded no relevant utility data for paediatric and adult patients with NF1 PN, nor for their families and carers. As such, a *de novo* utility study was conducted to estimate utility values for the population of relevance to this submission (as described below).

Table C30. Summary of studies reporting HRQoL data identified in the economic SLR

Source (Study ID)	Study population (N)	Setting	Methods of elicitation & valuation	Appropriateness of study for cost-effectiveness evaluation
Gross 2020[18, 19] (SPRINT Phase II Stratum I)	Paediatric patients aged 2–18 years with symptomatic, inoperable PN associated with NF1 (N=50). **Intervention** Patients were treated with selumetinib 25 mg/m^2, every 12 hours, with 28-day cycles.	US; outpatient paediatric oncology clinic.	PedsQL scale for measurement of patient HRQoL. Children from 8–18 years of age completed the PedsQL self-report version, and parents or legal guardians of children from 2–18 years of age completed the parent proxy version of the PedsQL.	**Consistency with NICE reference case:** No generic, general-population, preference-based instruments were included in SPRINT. Thus, no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem:** Fully aligned with the decision problem (but limited to up to three years of follow-up).
Hamoy-Jimenez 2020[152]	Adult patients meeting clinical diagnostic criteria for NF1 and/or having genetically confirmed NF1 (N=162).	Canada; academic clinic.	HSUV were assessed using the EQ-5D-5L. A Canadian valuation algorithm was used to estimate utility scores.[153]	**Consistency with NICE reference case**: Health state utility values were elicited using the EQ-5D-5L. The study took place in Canada, and valued utilities using a Canadian value set, which may not be directly relevant to clinical practice in the UK. **Relevance to the decision problem**: The study included adult patients with NF1. Not all patients had PN, and it was unclear if PN are inoperable and symptomatic, which deviates from the decision problem.
Lai 2019[25]	Eligible patients were aged 8–17 years old, had a confirmed diagnosis of NF1, had at least one PN in any location (symptomatic/	US	HRQoL was assessed using PROMIS, which was completed by the patient. HRQoL was also assessed using the NeuroQoL questionnaire.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could

	asymptomatic) and were fluent in English (N=140).			be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem**: Patients included were paediatric and had NF1 with inoperable and progressive PN, aligned with the decision problem. However, both symptomatic and asymptomatic patients were included which does not align with the decision problem.
Ren 2020[154]	Eligible patients were three years or older and had a diagnosis of NF1 PN, mix of craniofacial and non-craniofacial PNs (N=27).	China	HRQoL was measured using the INF1-QOL questionnaire.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem:** Patients included were NF1 patients with PN, which is aligned to the decision problem; however, this study included a mix of adults and children, limiting its applicability. It is also unclear whether all PN are inoperable and symptomatic, which further limits relevance to the decision problem.
Rosser 2018[155]	NF1 patients with symptomatic and inoperable PNs, aged >16 years (N=38).	US	HRQoL was assessed using the NF1 PedsQL. HRQoL was assessed at one timepoint, before patients received treatment.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis.

				Relevance to the decision problem: Patients included were NF1 patients with inoperable and symptomatic PN, which is aligned to the decision problem; however, the study included a mix of adults as well as children, limiting the applicability to the decision problem.
Weiss 2014 (NCT00634270)[156]	Patients aged ≥3 years with a diagnosis of NF1 and an unresectable PN with the potential to cause significant morbidity. Patients evaluated did not have evidence of progressive PNs. Of the 13 patients enrolled, nine were evaluated by self-reported HRQoL questionnaires. **Intervention** Sirolimus; 0.8 mg/m2, oral, twice/day, followed by subsequent pharmacokinetically guided dosing to achieve a trough blood concentration of 10–15 ng/ml.	US	**PedsQL 4.0**: HRQoL was assessed using the self-report form for children, and proxy form for parents. **FACT-G**: HRQoL of adult patients was assessed using the FACT-G questionnaire. All QoL measures were assessed at baseline and after six courses of sirolimus therapy.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem**: Patients included paediatric and adult patients with NF1 and inoperable PN. It is unclear whether the patients were symptomatic. As such the study is not aligned to the decision problem.
Widemann 2014 (NCT00021541)[41]	Children and young adults ≥3 and ≤25 years with a clinical diagnosis of NF1 and unresectable, measurable, progressive PNs with the potential to cause significant morbidity (N=60). Patients who underwent prior surgery for their progressive PNs were eligible provided the residual tumour was measurable. **Intervention**	US	**IPI Scale:** Parent total scores for participants on placebo were compared with scores for participants receiving tipifarnib.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem:** Patients included were NF1 patients with inoperable PN; however, the study included a mix of adults and paediatric patients, and is unclear whether PN are

	Tipifarnib, 200 mg/m2 orally every 12 hours, for 21 days followed by seven days' rest. Placebo, same regimen as intervention.			symptomatic, limiting the applicability to the decision problem.
Wolkenstein 2009[157]	Records from families with at least one child aged 8–16 years. CDLQI questionnaire scores were available from 75 children, of whom five had NF1 PN.	France	HRQoL was assessed using the French version of the CDLQI.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem**: The patients considered have NF1 and PN and are paediatric patients, so are relevant to the decision problem. However, it is unclear whether the PN are inoperable and symptomatic, limiting relevance to the decision problem.
Wolters 2015[19]	Children and adolescents 6–18 years of age with NF1 and PN. Patients were enrolled from a natural history protocol study at the NCI (N=60). Eligibility criteria included diagnosis of NF1 according to the NIH Consensus Conference criteria or a confirmed NF1 germline mutation.	US	HRQoL was assessed using the IPI form. Carers completed the forms for all participants, and parallel self-report forms were completed by adolescents (ages 10–18) and adults >18.	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. **Relevance to the decision problem:** Patients included have NF1 PN and are a paediatric population, so are relevant to the decision problem. It is unclear whether the PN are inoperable, limiting relevance to the decision problem.

Abbreviations: CDLQI: Children's Dermatology Life Quality Index; EQ-5D-5L: EuroQol five dimensions five levels questionnaire; FACT-G: Functional Assessment of Cancer Therapy – General; HRQoL: health-related quality of life; HSUV: health-state utility values; ID: identification; IPI: Impact of Pediatric Illness Scale; INF1-QoL:

impact of NF1 on Quality of Life; NCI: National Cancer Institute; NeuroQoL: Quality of Life in Neurological Disorders; NF1: neurofibromatosis type 1; NICE: National institute for Health and Care Excellence; NIH: National Institutes of Health; PedsQL: Pediatric Quality of Life InventoryTM; PN: plexiform neurofibroma; PROMIS: Patient-Reported Outcomes Measurement Information System; US: United States.

Time-trade-off (TTO) study

Given the rarity of NF1 PN, there is limited published evidence on the HRQoL burden throughout the disease course. The HRQoL data from SPRINT are only available for patients treated with selumetinib, and for up to three years of follow-up; no alternative utility values have been reported for NF1 PN patients. As such, there are insufficient data to address the entire patient lifetime in a comparative cost-effective analysis of selumetinib versus current clinical management.

To resolve the evidence gaps and to facilitate the cost-effectiveness analysis, a vignette-based time-trade-off (TTO) study was commissioned by AstraZeneca and conducted by Acaster Lloyd Consulting. The purpose of the TTO study was to elicit utility weights for different health states associated with patients with NF1 PN. Such studies are appropriate, and indeed have been accepted in several previous NICE appraisals, where there are no EQ-5D values available from the relevant clinical trial or published literature. The TTO method is a choice-based method commonly used to elicit health state utility weights for a variety of disease states. Disease states are defined using vignettes, which include a description of all important and relevant aspects of HRQoL. Participants are tasked with choosing between ten years in the target health state against the prospect of X years in full health. The time in full health is then varied until the point is reached where participants are indifferent about the choice.[158, 159]

Methodologies for developing and conducting vignette-based studies are well-documented. The TTO vignettes in this study were developed in line with NICE recommendations for generating utility estimates for health states to use vignettes when EQ-5D data are unavailable.[158] Descriptions that appropriately and accurately reflect the disease course of NF1 PN over a patient's lifetime were produced, to avoid some of the limitations of previous vignette studies. This process included conducting an additional targeted literature review of HRQoL in NF1 PN, and soliciting feedback from patients (n=8), parents/carers (n=6) and UK clinical experts (n=4).[28]

Further details of the TTO study are described below, with supplementary information provided in the Appendix (Section 17.7.4).

Study objectives

The non-interventional, *de novo* TTO study had three key objectives:

1. To develop and validate the content of draft NF1 PN patient health state vignettes (**Part I**)

2. To explore the NF1 PN patient and parent/carer burden (**Part II**), with a focus on the impact of PN on patient and parent/carer HRQoL

3. To estimate health state utilities associated with NF1 PN disease states using the TTO methodology (**Part III**)

Part I: Development and validation of vignettes

In Part I, health state vignettes were developed to describe typical patients with NF1 PN in terms of their symptoms, functioning, HRQoL, and if on treatment, any notable side

effects they experience. Vignettes were developed for both children and adults, by PN location (unspecified location, facial, trunk and leg), and by treatment status (treated with selumetinib, not treated with selumetinib, and off selumetinib due to disease progression). Given the heterogeneity of NF1 PN, the health states associated with an unspecified PN location are deemed most appropriate to reflect a 'typical' patient in the cost-effectiveness analysis.

In line with recommendations by the NICE DSU, vignette descriptions were informed by a targeted literature review; in addition, feedback on the health state vignettes was sought from patients, parents/carers and key clinical experts in NF1 PN, in order to ensure that the experience of patients were accurately represented (neither exaggerated or understated) within the vignettes.[159] Draft vignettes were revised iteratively after interviews with the clinical experts, and subsequently, after adult patient and parent/carer interviews (described in Part II).

Part II: Qualitative interviews

In Part II, qualitative semi-structured interviews were conducted with adult patients (aged ≥18 years) with NF1 PN, and parents/carers of paediatric patients (aged <18) with NF1 PN. Interview materials were informed by a targeted literature review. There were two objectives within Part II:

- To validate the vignettes developed in Part I; and
- To explore the patient and parent/carer burden and HRQoL of NF1 PN and to identify relevant issues affecting HRQoL from the patient and parent/carer perspective.

The aim was to recruit a total of six to seven adult patients, and six to seven parents/carers. Participants were recruited through the patient association Nerve Tumours UK (NTUK) using recruitment adverts/invitation letters. If interested, potential participants could contact the researchers for further information about the study. Potential participants were then asked to complete a brief screening questionnaire in order to confirm that they met the inclusion criteria and flexible quotas set to achieve purposive sampling, with the aim to include participants with a range of characteristics relevant to NF1 PN. The inclusion criteria for participants for the qualitative interviews were as follows:

- Having had a medically confirmed diagnosis of NF1 PN (self-reported) AND/OR being a parent/carer of someone with a medically confirmed NF1 PN diagnosis (proxy-reported)
- NF1 PN patient has never been treated with selumetinib, nor with binimetinib, cobimetinib, mirdametinib or trametinib (off label treatments sometimes used in this population)
- NF1 PN patient is not currently pregnant
- Participant is aged ≥18
- Participant is a resident of the UK

- Participant is willing and able to give their informed, written consent to take part in a 60–75 minutes recorded interview (including the ability to read and write without help from others)

Informed consent was obtained prior to all interviews via email, with consent re-confirmed verbally at the start of the interview.

Eight adult patients with NF1 PN and six parents/carers of patients with NF1 PN were interviewed. All interviews were conducted using a semi-structured interview guide by experienced interviewers, with interviews conducted individually over the telephone or via an online video call lasting approximately one hour each.

Part III: Estimation of health state utilities

Finally, in Part III of the study, the vignettes developed in Part I and II were used in interviews with the general public to estimate health state utilities for NF1 PN using the TTO method.

Participant recruitment

Members of the general public were recruited through (online) advertisements, informal and online social networks and/or snowballing. Interviewers were set quotas to ensure that the sample was representative of the UK population in terms of age, sex and ethnicity. Participants were eligible if they were adults (aged ≥18 years).

100 members of the UK general public completed a visual analogue scale (VAS) and TTO assessment, including the lead-time method. All TTO interviews were conducted using online video calls, with interviews conducted by trained TTO interviewers.

Valuation exercises

Participants used physical printed versions of the vignettes in the interview. All interviews were conducted by trained TTO interviewers. The first exercise used a VAS ranging from 0 (worst possible state) to 100 ‘full health’. To ensure participants had a good understanding of the task, participants first ranked two practice vignettes ahead of commencing the full exercise. Health state vignettes and ‘dead’ were then presented one-by-one. A ‘dead’ vignette, described as ‘Dead’, was included to allow participants to indicate if they considered any of the vignettes to be worse than dead. Following the VAS exercise, participants completed a TTO interview for all vignettes. For each vignette, the interviewer recorded the utility value at the point of indifference. If participants rated any vignette as worse than dead, they were asked to confirm that they believed that this was the case before completing the lead time TTO procedure for states deemed worse than dead.

Results

While NF1-PN is a heterogenous disease with impact of symptoms varying according to PN location (see Section 6.1), the relative differences between untreated and treated values did not differ significantly between the alternatively specified PN locations (as shown in Table C35), validating and supporting the use of the unspecified PN location

vignettes. Therefore, the finalised vignettes, participant details and relevant results for the cost-effectiveness analysis are presented below, which are considered representative of the average utility in the NF1 PN patient population:

- Untreated paediatric patient with unspecified PN location (hereafter referred to as paediatric patient under current clinical management), and

- Treated paediatric patient with unspecified PN location (hereafter referred to as paediatric patient with selumetinib)

Table C31. Finalised TTO study vignettes

Paediatric patient without selumetinib
You have a life-long genetic condition that causes lumps to grow in any part of the body, causing a range of symptoms. You have one main, large lump with an irregular shape.
You receive no active treatment for your main, large lump. Your condition is monitored by your care team and you receive supportive care to help manage some of your symptoms.
Your condition is deteriorating over time.
The way you look is affected by your large lump. Your lump continues to grow.
You have some difficulties with movement, strength and coordination. Your difficulties moving the area around your large lump are deteriorating over time.
You often experience pain/discomfort in the area around your large lump. The pain/discomfort that you experience can interfere with your daily activities and sleep. You use pain medication to manage your pain. Sometimes your pain medication does not control your pain.
You occasionally feel anxious or depressed. You worry about how your condition will progress in the future.
You feel self-conscious about your condition and sometimes experience bullying. You sometimes find it difficult to communicate your condition to others.
You sometimes need help looking after yourself.
You have some problems with understanding, memory, learning and attention. You may require additional help at school/work as well as support with developing and maintaining friendships.
Paediatric patient with selumetinib
You have a life-long genetic condition that causes lumps to grow in any part of the body, causing a range of symptoms. You have one main, large lump with an irregular shape.
You receive an oral medication twice a day for your main, large lump. Your condition is monitored by your care team and you receive supportive care to help manage some of your symptoms.
With treatment your condition is improving.
Your treatment occasionally causes you to have skin rashes.
The way you look is affected by your large lump. Since you started treatment, you have noticed slight improvements in the size and appearance of your lump.
You have some difficulties with movement, strength and coordination. Since you started treatment, you are able to move the area around your large lump slightly more freely.
You sometimes experience pain/discomfort in the area around your large lump. The pain/discomfort that you experience can interfere with your daily activities and sleep. You use pain medication to manage your pain.
You occasionally feel anxious or depressed. You are, however, enjoying life and feel optimistic about the future.

You feel self-conscious about your condition and sometimes experience bullying. You sometimes find it difficult to communicate your condition to others.
You sometimes need help looking after yourself. Since your condition has stabilised, you have needed less help with your daily activities.
You have some problems with understanding, memory, learning and attention. You may require additional help at school/work as well as support with developing and maintaining friendships.

Sample size and characteristics

Summary characteristics of participants (n=100) who took part in the TTO valuation intervals are presented in Table C32, along with UK general population data for age, sex and ethnicity (from the most recent, available UK census data).[160, 161]

The characteristics of the respondents were broadly similar to the broader UK population in terms of age, sex and ethnicity. In line with the NICE reference case, the population recruited to value the vignette health states was a representative sample of the UK general public.

Table C32. Sample characteristics from valuation interviews (n=100)

Characteristic		UK sample for TTO valuation (N=100)	UK population
		Mean (SD)	Median
Age		[redacted]	39.4
		n (%)	%
Sex	Male	[redacted]	49%
	Female	[redacted]	51%
Ethnicity	White	[redacted]	86%
	Asian	[redacted]	8%
	Black	[redacted]	3%
	Mixed	[redacted]	2%
	Other	[redacted]	1%

Source: Lo et al.,[160] ONS[161]

VAS ratings

The mean VAS ratings for the health state vignettes are presented in Table C33. Table C34 shows the TTO ratings for the health stage vignettes.

Table C33. VAS ratings for health state vignettes (n=100)

Health state	Mean (SD)	SE	95% CI
Paediatric patient without selumetinib	[redacted]	[redacted]	[redacted]
Paediatric patient with selumetinib	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; SD: standard deviation; SE: standard error; VAS: visual analogue scale.

Table C34. TTO ratings for health state vignettes (n=100)

Health state	Mean (SD)	SE	95% CI
Paediatric patient without selumetinib	[redacted]	[redacted]	[redacted]
Paediatric patient with selumetinib	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; SD: standard deviation; SE: standard error; TTO: time-trade-off.

The use of utilities from health states representing an unspecified PN location for the economic analysis has been justified earlier in this section. The difference in utility values for patients treated with and without selumetinib were consistent across different PN locations, with the difference ranging from [redacted] to [redacted] (Table C35). This supports the use of utilities for the health states with an unspecified PN location, on the basis of being most representative of the NF1 PN patient population as a whole.

Table C35. Utility value differences with and without selumetinib

PN location	Difference in utility value with and without selumetinib
Unspecified (base case)	[redacted]
Face	[redacted]
Trunk	[redacted]
Leg	[redacted]

Abbreviations: PN: plexiform neuroma.

10.4.3 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

As described in Section 10.4.1, there are currently no studies that describe HRQoL over the disease course of NF1 PN, and no dataset is available to depict the impact via utility values over patients' lifetimes for use in the cost-effectiveness analysis. In the absence of appropriate utilities data, alternative approaches were deemed necessary for a robust analysis. The TTO study was conducted to address the evidence gap, with the study providing relevant utility values for the model health states for both the treated and untreated NF1 PN population.

10.5 Adverse events

10.5.1 Please describe how adverse events have an impact on HRQoL.

Selumetinib monotherapy has a generally predictable and manageable safety profile in paediatric patients with NF1 PN, and AEs were usually mild or moderate in severity.[58] It can therefore be assumed that the adverse events will have a minimal impact on HRQoL. Further details of the AEs experienced by patients receiving selumetinib are provided in Section 9.7.

For completeness, the cost of AEs, while minimal, has been included in the cost-effectiveness analysis (see Section 12.2.4).

10.6 Quality-of-life data used in cost-effectiveness analysis

10.6.1 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

NF1 PN patient utility

The utility values used in the cost-effectiveness analysis were derived from the TTO study described in Section 10.4 and are presented in Table C36. The TTO study was conducted following NICE DSU guidance, and is consistent with the NICE reference case. Utility values for patients with an unspecified PN location are representative of the average utility experienced by a typical patient with NF1 PN, given the variety of PN locations that may be present (see Section 6.1 for further details).

Table C36. Summary of HRQoL values for cost-effectiveness analysis

State	Utility value	Confidence interval	Justification
Paediatric patient with selumetinib	[redacted]	[redacted]	In the absence of suitable utilities from clinical trials or the published literature, a de novo analysis TTO study was considered appropriate
Paediatric patient without selumetinib	[redacted]	[redacted]	

Parent/carer disutility

As described in Section 7.1 and 7.2, **the HRQoL of parents, families and carers of NF1 PN patients is also substantially impacted**.[24, 25] To better understand the type and extent of impact on parents and families, feedback was sought from clinical experts in NF1 PN across the UK and several European countries.[27, 28] The clinical experts confirmed that there is a substantial HRQoL impact on parents and families, through the following:

- **Emotional distress, constant worry and anxiety** experienced by parents, especially when their child has uncontrolled persistent or rapid PN growth and there are no treatment options.
- **Social isolation** associated with their child's disfigurement and/or functional limitations due to PNs.
- **Stress and mental burden** associated with providing a range of support including coordinating and managing appointments across multiple clinical specialists, having a key role in the frequent monitoring of disease and daily symptom management, and providing often have specific cognitive and behavioural issues.

- Impact on quality of life through **disrupted social activities and time off work** that is common for parents needing to care for their child under certain circumstances, such as for being sent home from school, or for attending appointments.

Clinical experts clarified that **such support required by NF1 PN patients is not limited by age**; many of these factors continue to contribute to the QoL burden for parents, families and carers even when the patient is an adult. [28] One clinical expert noted that **in some cases, parents and families may seem to be more emotionally affected than patients themselves due to the reasons above**.[28]

Feedback from the clinical experts confirmed that the HRQoL burden of parents, families and carers should be considered in the analysis.[28] However, there are currently no direct estimates of the impact on the HRQoL and no data were identified through the SLR. The base case analysis therefore applied the following assumptions:

- Parents/carers experience the same relative HRQoL decrement as for patients.

- Starting from a mean age of parents of 30.6 years at childbirth based on ONS statistics,[162] a general population utility value is determined using the regression algorithm from Ara and Brazier (2010); this represents the maximum parent/carer utility of a patient receiving selumetinib. Parent age is tracked in the model and utilities are adjusted accordingly, each model cycle.[163]

- The relative mean difference in utility between the selumetinib and current clinical management patient cohorts is calculated. This is used to weight and calculate the parent/carer utilities in the BSC arm.

- The impact is included until the patient reaches the age of 18 – after which, it is conservatively assumed that no further support from parents and carers are required.

In the absence of data measuring the direct HRQoL impact on parents, families and carers, the methods for incorporating such burden is subject to discussion. Alternative assumptions have been explored in scenario analyses to test the impact of including parent/carer HRQoL on the results (see Section 12.2 and 12.4 for further details):

- Many other conditions reflect the considerable burden of disease experienced by parents/carers of paediatric patients. An alternative absolute utility decrement of 0.08 per parent/carer was identified, based on the mean of utility values reported in HST11 (Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations). While this decrement is not specific to NF1, it incorporates parent/carer utilities for a wide range of patient health states, therefore representing the overall impact on the parent/carer.[164] This value is considered in scenarios related to parent/carer disutility; in addition, the analysis explored several other scenarios related to parent/carer disutility (see Section 12.4.1).

- Additional scenarios that vary the proportion of HRQoL decrement experienced between parents and patients' utility values (i.e. assuming 50% or 75% impact on parents/carers instead).

- Various assumptions tested on the duration of parent/carer HRQoL impact included, such as limiting the duration until the patient reaches 24 years of age, or until the carer themselves reach an age of 64 years old.

10.6.2 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Initial clinical expert interviews

During the early development of the cost-effectiveness model, one-to-one interviews were conducted via online video calls with four clinical experts in NF1 PN across the UK and Europe. All clinical experts received a short document summarising the aims of the interview and key data/concepts for discussion ahead of the calls. The interview was conducted according to a structured discussion guide, and sought initial feedback on the following topics:

- Qualitative evidence around the burden of NF1 PN on patients, parents, families and carers.
- Impact of NF1 PN on patients' HRQoL over time (i.e. with age) under current clinical management and with selumetinib.
- Validation of parametric models fitted to TTD data from the SPRINT study.

Vignette feedback and validation by clinical experts

Clinical experts were also engaged in the TTO study described in Section 10.4. Interviews were conducted by Acaster Lloyd Consulting Ltd via online video call or telephone to obtain feedback on the draft vignettes. Interview guides were prepared with questions designed to validate and refine the content of the vignettes (available in Appendix 17.7.4). Each clinical expert had the opportunity to provide feedback on all health state vignettes which was used to develop and finalise the vignettes.

Final UK clinical expert validation exercises

Further clinical expert input was sought in order to validate the clinical rationale underlying various assumptions required in the economic analysis from a specific UK perspective.[28] A total of four clinical experts were consulted, with 1-hour teleconferences carried out in July 2021. The clinical experts comprised of two paediatric oncologists, one lead nurse, and one geneticist; the latter two experts are involved in 'lifespan' service and see both children and adults with NF1 PN. The clinical experts were selected on the basis that they were all based in England and had direct experience of treating patients with NF1 PN. All of the experts had direct experience of selumetinib use in their centre.

Feedback was obtained via structured interviews including questions on the following topics:

- The clinical course of symptomatic inoperable NF1 PN and the current clinical pathway for patients
- Comparability of the SPRINT study population with UK setting
- The clinical benefit of selumetinib and any safety/tolerability considerations
- Wider aspects of care for patients, parents and carers
- The link between the disease course of NF1 PN and HRQoL over time, and the potential impact selumetinib as incorporated in the economic model

10.6.3 Please define what a patient experiences in the health states in terms of HRQoL. Is it constant or does it cover potential variances?

PN can result in symptoms of pain, motor dysfunction, bowel, bladder or airway complications, visual impairment, or disfigurement.[19, 25, 26] Due to the heterogeneous manifestations of NF1 PN, which often depends on both the location and size of PN, and limited available data from SPRINT Phase II Stratum I, a simplifying assumption is required to model the overall impact of NF1 PN on patients' HRQoL over time and the potential benefit of selumetinib . The underlying clinical rationale follow the evidence discussed in Section 7.1, Section 9.6 and Section 10, while details regarding the incorporation of HRQoL in the cost-effectiveness model are provided in Section 12.2.

10.6.4 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

As noted above, due to the heterogeneous nature of NF1 PN, the analysis incorporates the overall impact of PN-associated morbidities, which implicitly includes the impact of health effects such as pain, motor dysfunction, bowel, bladder or airway complications, visual impairment, or disfigurement on patients' HRQoL. This broad approach is appropriate for NF1 PN and does not require assumptions about including or excluding specific health effects.

10.6.5 If appropriate, what was the baseline quality of life assumed in the analysis, if different from health states? Were quality-of-life events taken from this baseline?

The baseline value in both arms of the model is that of a paediatric patient under current clinical management or best supportive care (BSC) based on the TTO study ([redacted]).

10.6.6 Please clarify whether HRQoL is assumed to be constant over time. If not, provide details of how HRQoL changes with time.

In the BSC arm, patients' HRQoL remains constant over time for the duration of the analysis as the elicited utility value ([redacted]) already represents the condition of these patients. No further decrements due to events are required.

The benefit of selumetinib is modelled via improved utility values from baseline (Section 12.2).

The impact of selumetinib on patients' HRQoL is incorporated as an improvement in the utility value to [redacted] within one year, and remains constant for the duration of the analysis for patients who maintain partial response or stable disease. If a patient on selumetinib experiences substantial PN growth or progression (defined as a ≥20% increase in tumour volume from baseline), their utility value declines downwards back to baseline, over a period of five years.

Within the model, all utility values are also adjusted age-related disutility, based on Ara and Brazier (2010).[163] The regression algorithm to calculate general population utility as the population ages is:

$$EQ5D = 0.9508566 + 0.0212126 * male - 0.0002857 * age - 0.0000332 * age^2$$

10.6.7 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

No.

10.7 Treatment continuation rules

10.7.1 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

As per the SmPC for selumetinib, paediatric patients can start selumetinib treatment following NF1 diagnosis and the identification of symptomatic, inoperable PN.[37] Treatment with selumetinib should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. Patients would be expected to discontinue treatment with selumetinib upon reaching the age of 18, in line with the paediatric license. [37]

It has been demonstrated that typically, PN grow most rapidly in young children, with the growth rate slowing as patients age. By the time a patient reaches the age of 16-18 years, PN growth tends to halt or slow to a level of minimal growth, as illustrated in Figure C20 . This gives a natural indication of when the magnitude of impact of PN growth and tumour size may plateau, which is applicable with or without selumetinib.[85]

Patients enter the model at an average age of [redacted] years, following the mean starting age of patients in SPRINT Phase II Stratum I.[34] For patients in the selumetinib arm, treatment discontinuation is modelled via parametric distributions fit to patient-level data of time-to-discontinuation (TTD) from SPRINT Phase II Stratum I. Given the average starting age of 10 years, a duration of approximately 8 years is likely to reflect the maximum duration of treatment realised in clinical practice for children and adolescents. This is highly justifiable, with the average duration of treatment in the SPRINT study being far below this maximum applied in the model (Section 9.7).

Figure C20. Change in PN growth from individual patient profiles, over 5 years by age group

Source: AstraZeneca Data on File.[85]

Section D – Value for Money and cost to the NHS and personal social services

Summary of Section D11

- A single SLR was conducted in January to February 2021, in order to identify all literature published on HRQoL, cost and resource use, and economic evaluations in paediatric and adult patients with NF1, as well as that of their family and parents/carers. In light of the small body of evidence for NF1, a broad search strategy was employed
- A total of ten publications reporting on nine unique studies were identified reporting relevant HRQoL data, and four publications reporting on four unique studies were identified reporting relevant cost and resource use data; no economic evaluations were identified. A de novo cost-effectiveness analysis was therefore undertaken

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished

data. The search strategy used should be provided as in section 17.3.

A single SLR was conducted in January to February 2021, in order to identify all literature published on HRQoL, cost and resource use, and economic evaluations in paediatric and adult patients with NF1, as well as that of their family and carers. Given that there is a small body of evidence surrounding NF1, a broad approach was taken to maximise the searches.

The eligibility criteria for this SLR is provided in Table D in Section 11.1.2 and a record of included studies is given in Section 11.2. Full details of the SLR methodology taken are provided in the Appendix (Section 17.4). In summary, the following steps were undertaken:

- A search of the following electronic databases:
    - Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (searched via the Ovid SP platform, 1946 to January 25, 2021)
    - Embase (searched via the Ovid SP platform, 1974 to 25 January 2021)
    - The Health Technology Assessment Database (HTAD), (searched via the University of York Centre for Reviews and Dissemination [CRD] platform, to Issue 4 of 4, October 2016)
    - The NHS Economic Evaluation Database (NHS EED), (searched via the University of York CRD platform, to Issue 2 of 4, April 2015)
    - International HTA Database (searched via the International Network of Agencies for Health Technology Assessment [INAHTA] website, to January 25, 2021)
- A manual search of proceedings from the following conferences:
    - International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – International and European meetings, 2018, 2019 and 2020
    - Joint Global Neurofibromatosis Conference (JGNC) – 2018 (this event combined the Children's Tumor Foundation NF Conference and European Neurofibromatosis Meetings in that year)
    - Children's Tumor Foundation NF Conference – 2019 and 2020
    - European Society for Medical Oncology (ESMO) – 2018, 2019 and 2020
    - American Society of Clinical Oncology (ASCO) – 2018, 2019 and 2020
    - International Symposium on Pediatric Neuro-Oncology (ISPNO) – 2018 and 2020

    - American Society of Pediatric Hematology/Oncology (ASPHO) – 2018, 2019 and 2020

- Manual searches of the bibliographies of all relevant SLRs, [N]MAs), HTAs and economic evaluations identified during the course of the review
- A search of the following HTA body websites for relevant HTA submissions from the last 10 years:
    - All Wales Medicines Strategy Group (AWMSG)
    - National Centre for Pharmacoeconomics (NCPE)
    - National Institute for Health and Care Excellence (NICE)
    - Scottish Medicines Consortium (SMC)
- Searches of the following websites to identify any inputs relevant to cost-effectiveness modelling:
    - The Cost-Effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center
    - The University of Sheffield Health Utilities Database (ScHARRHUD)
    - The EuroQol 5 Dimensions (EQ-5D) Publications Database
    - The Paediatric Economic Database Evaluation (PEDE) database
- Manual searches of internal AstraZeneca materials, including:
    - A TLR conducted in 2019 on NF1 PN clinical studies
    - A TLR conducted in 2020 to capture HRQoL instruments in NF1

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature.

The inclusion and exclusion criteria are given in Table D below. Given that there is a small body of evidence surrounding NF1, broad inclusion and exclusion criteria were used.

Table D1. Selection criteria used for health economic studies

Domain	Economic Evaluations		HRQoL		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
Population	• Paediatric or adult patients with NF1	• Paediatric and/or adult patients without NF1	• Paediatric or adult patients with NF1 with PN • Paediatric or adult patients with NF1 without PN for whom HSUVs are reported[a] • Caregivers/family of patients with NF1 with PN	• Paediatric and/or adult patients without NF1 • Paediatric or adult patients with NF1 without PN for whom only HRQoL values are reported[a]	• Paediatric or adult patients with NF1 with PN • Caregivers/family of patients with NF1 with PN	• Paediatric and/or adult patients without NF1 • Paediatric or adult patients with NF1 without PN[b]
Intervention	• Any or none					
Comparator	• Any or none					
Outcomes	• ICERs • Cost per clinical outcome • Total QALYs • Total DALYs • Total LYGs • Total costs • Incremental costs and	• Studies not presenting relevant outcomes for the population of interest	Any utilities or HRQoL data, if measured by a formal validated tool or instrument, including but not limited to: • EQ-5D-5L • Standard gamble • Time trade-off • SF-36 • PedsQL (including	• Studies not presenting relevant outcomes for the population of interest.	Direct costs and resource use, including: • Drug cost • Administration cost • Hospitalisation cost • Monitoring costs • Indirect costs and	• Studies not presenting relevant outcomes for the population of interest

Domain	Economic Evaluations		HRQoL		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
	QALYs/DALYs		NF1 module) • PROMIS • TACQOL		resource use, including: • Productivity loss • Home adaptation • Travel costs	
Study Design	• Cost-utility • Cost-effectiveness • Cost-consequence • Cost-benefit • Cost-minimisation	• Any other types of analysis	• Any original research study	• N/A	• Any original research study, including budget impact models and cost-of-illness studies	• N/A
	SLRs or (N)MAs of relevant study designs were included at the title/abstract screening stage for the purpose of identifying any additional studies not identified in the database searches, but were ultimately excluded at the full-text review stage.					
Publication type	**Inclusion:** • Journal articles presenting original research • HTAs • Conference abstracts published in or since 2018 **Exclusion:** • Articles not presenting original research, e.g. narrative reviews, guidelines, commentaries or opinion pieces, editorials • Conference abstracts published before 2018					
Other considerations	**Inclusion:** • Human subjects • Any geographic location **Exclusion:** • In vitro/ preclinical studies/animal studies					

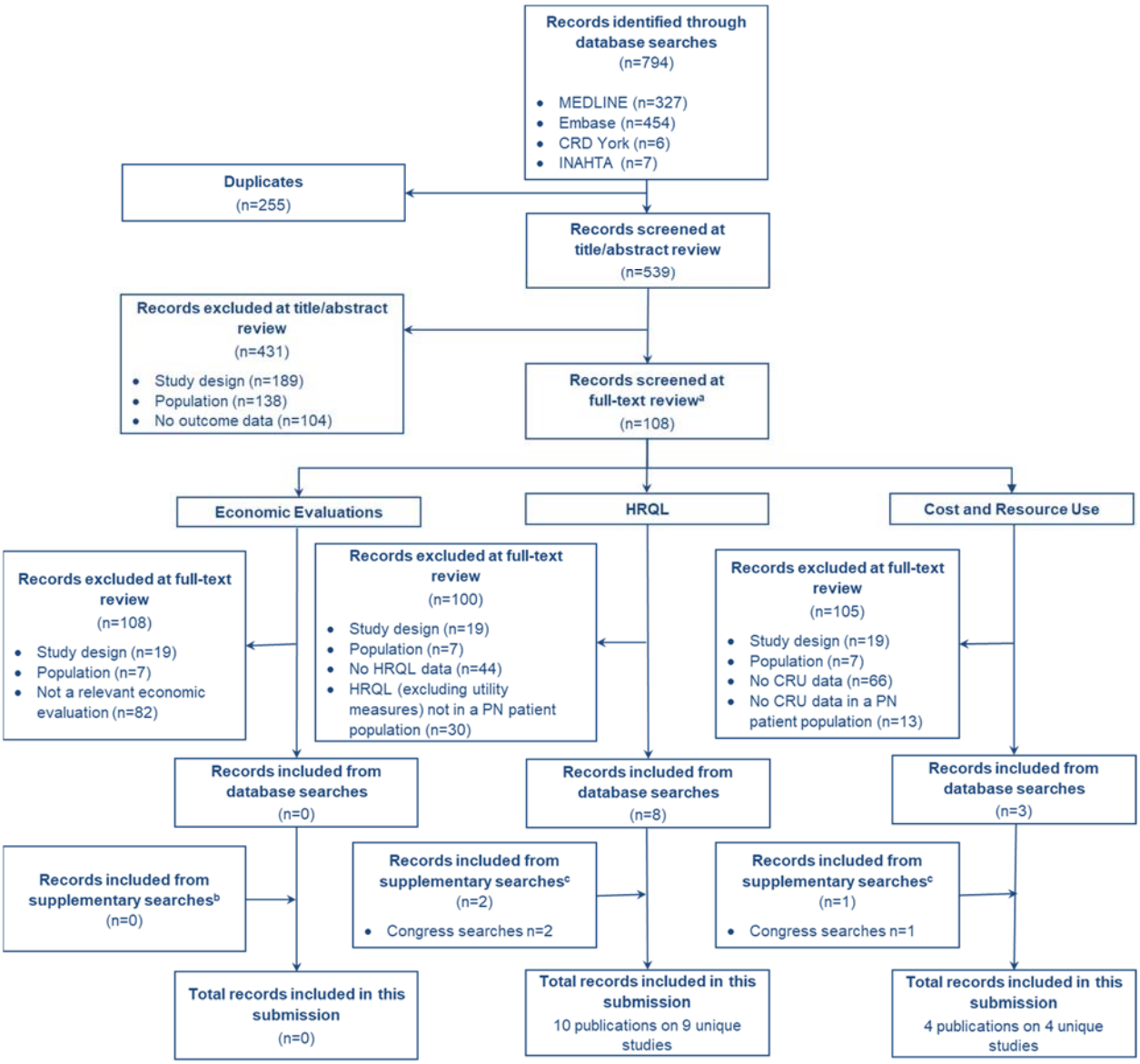
Footnotes: [a]Records that presented any HRQoL values for paediatric or adult patients with NF1 without PN were included at title/abstract review then excluded at full-text review due to the high volume of relevant data identified; records presenting HSUV values for paediatric or adult patients with NF1 without PN were included at both review stages [b]Records that presented any CRU data for paediatric or adult patients with NF1 without PN were included at title/abstract review then excluded at full-text review due to the high volume of relevant data identified.
Abbreviations: CRU: cost and resource use; DALY: disability-adjusted life-year; EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels; HRQoL: health-related quality of life; HSUV: health-state utility value; HTA: Health Technology Assessment; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NF1: neurofibromatosis type 1; PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma; PROMIS: Patient-Reported Outcomes Measurement Information System; QALY: quality-adjusted life-year; SF-36: Short Form 36; TACQOL: Netherlands Organization for Applied Scientific Research Academic Medical Centre (TNO AZL) Children's Quality of Life.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the SLR is presented in Figure D. In the SLR, 794 records were retrieved from the electronic database searches, of which 255 were duplicates, meaning 539 novel records were screened at the title/abstract review stage. Subsequently, 108 full publications were screened at full-text review. Following this review, eight publications were included in the HRQoL steam, three in the cost and resource use stream and zero in the economic evaluations stream. Tables listing the studies included in the SLR can be found in Section 10.4 and 11.2 for the HRQoL and cost and resource use stream respectively. Tables listing the studies excluded in the SLR following the full-text review stage, alongside reasons for exclusion can be found in the Appendix (Section 17.4.8).

Supplementary searching identified an additional three records that met the inclusion criteria, meaning a total of ten publications reporting on nine unique studies were identified reporting relevant HRQoL data, four publications reporting on four unique studies identified reporting relevant cost and resource use data, and zero economic evaluations were identified.

Figure D1. PRISMA flow diagram for the economic SLR



Footnotes: [a]All records screened at full-text review were reviewed against all three streams, some reported relevant data in more than one stream [b]1,192 records were identified through supplementary searches (congress searches, economic websites, HTA websites, bibliography searches, supplementary searches) and none were included [c]1,192 records were identified through supplementary searches, no records found for economic websites, HTA websites, bibliography searches and supplementary searches were included in this stream.
Abbreviations: CRD: Centre for Reviews and Dissemination; CRU: costs and resource use; HRQoL: health-related quality of life; HTA: health technology assessment; INAHTA: International Network of Agencies for Health Technology Assessment; PN: plexiform neurofibroma; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SLR: systematic literature review .

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

No relevant health economic evaluations were identified; a *de novo* cost-effectiveness analysis was required to estimate the cost-effectiveness of selumetinib versus established clinical management (consisting of best supportive care), for the treatment of paediatric patients with NF1 and symptomatic, inoperable PN.

12 Economic analysis

Summary of Section D12

Selumetinib represents a cost-effective use of NHS resources, with an ICER of £93,169 per QALY in the base-case analysis ([redacted]).

Summary of the *de novo* cost effectiveness model

- NF1 PN is a rare and highly heterogeneous disease that can present very differently between patients, both in the physical presentation and the associated symptomatology. Furthermore, due to limited availability of data, model structures such as full Markov state-transition and patient-level simulation models that are used across other disease areas were unfeasible

- A simplified AUC model structure was required, with the underlying clinical rationale and key assumptions validated by clinical experts in NF1 PN (Section 10.6.2 and 12.1).[28] Within this approach, patients occupy one of three health states: non-progressed (on or off treatment with selumetinib), progressed, or deceased

    - All patients in the selumetinib arm were assumed to remain on treatment until discontinuation, which was based directly on parametric extrapolation of TTD data from SPRINT; disease progression was modelled independently based on PFS data from SPRINT[18]

    - Survival over the modelled lifetime horizon was based on general population mortality and an SMR to account for the reduced life expectancy associated with NF1-related comorbidities

- Utility values accrued in the health states were derived from the TTO study (see Section 10.4), and were dependent on age and whether a patient was progressed or non-progressed; corresponding proportional utility benefits for parents/carers of patients receiving selumetinib were also included given qualitative evidence and feedback from clinical experts that highlighted the substantial impact on parents and families[28]

- Costs accrued in the heath states were dependent on whether a patient is on or off treatment with selumetinib; although minimal, the model also included costs associated with treatment-dependent AEs, pain medication and MRI scans

- Key assumptions and inputs used in the model were validated through one-to-one interviews with multiple UK clinical experts (Section 10.6.2 and Section 12.7)

Summary of the cost-effectiveness results

- The base case analysis (including the PAS price for selumetinib) resulted in an ICER for selumetinib of £93,169 per QALY gained. Selumetinib is expected to provide an additional [redacted] QALYs versus current clinical management, which is consistent with the benefit of associated lifelong impact of preventing PN growth

from childhood, where PN volume growth has been observed to be most rapid. These benefits are associated with an incremental cost of [redacted]

- One-way deterministic sensitivity analyses and probabilistic sensitivity analyses demonstrated that the model was largely robust to uncertainty in the majority of parameters. A wide range of scenario analyses were conducted to explore the impact of changing various assumptions (e.g. for TTD extrapolation, mortality, and patient and parent/carer QoL) with the results being overall consistent with the deterministic base case results

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

Selumetinib is indicated for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above (see Section 3). The modelled population is consistent with the decision problem and the licensed population.

The baseline characteristics for patients entering the economic model are based on the SPRINT Phase II Stratum I data, as outlined in Table D2.[18, 34]

Table D2. Key baseline characteristics of the modelled population

Parameters	Values	Purpose in the model
Female (%)	[redacted]	Used to implement all-cause mortality data (rates available by female/male) as described in Section 12.2
Age in years (mean [SD])	[redacted]	Tracked in the economic model at each model cycle, affects various inputs (e.g. age-adjusted utility values)
BSA in m^2 (mean [SD])	[redacted]	Required to determine the appropriate dose of selumetinib as detailed in Section 12.3

Abbreviations: BSA: body surface area; SD: standard deviation.
Source: AstraZeneca Data on File (CSR)[34]

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

In line with the final scope and decision problem for this appraisal, the cost-effectiveness of selumetinib is compared against current clinical management of patients with NF1 PN, which consists of only best supportive care (BSC). As there are currently no disease-modifying treatments, BSC is limited to symptomatic management (see Section 8.2 for further information).[11, 19, 33, 28]

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

A simplified AUC model structure was required for a robust analysis in light of data limitations in NF1 PN. Key underlying clinical rationale and assumptions for the economic model were validated by UK clinical experts in NF1 PN. This section provides a diagram and description of the model structure; further details regarding key justification for the model structure are provided in Section 12.1.4 and 12.1.5.

Based on the natural history of disease progression, patients may occupy one of the following three "states" at any time within the model, updated at each 1-year cycle over a lifetime horizon (Figure D2):

- Stable / non-progressive disease (stabilised or reduced PN growth; see below)
- Progressive disease (defined as ≥20% increase in size from baseline of PN or, if a patient had had a partial response, an increase of at least 20% from the best response, by volumetric MRI analysis in line with the REiNS criteria (Section 9.4.1)
- Deceased

Patients in the BSC arm do not receive any treatment (i.e. current clinical management consists of pain medications and symptom relief only) and enter the model with progressive disease, consistent with the natural disease course of NF1 PN.

All patients in the selumetinib arm are initially on treatment, and remain so until treatment discontinuation. Patients experience disease stabilisation within the first year of treatment and remain in the progression-free state until disease progression, which is modelled based on the PFS data from SPRINT Phase II Stratum I (see Section 9.6).[18] Treatment duration was modelled via parametric models fit to patient-level data of TTD from the SPRINT Phase II Stratum I (see Section 12.2.1). Given the paediatric license for selumetinib (i.e., until the age of 18), eight years is an approximate maximum duration of treatment that is highly likely to be realised in clinical practice and is more than sufficient, based on the duration of treatment recorded in the SPRINT study (see Section 9.7 and Section 10.7 for further details).

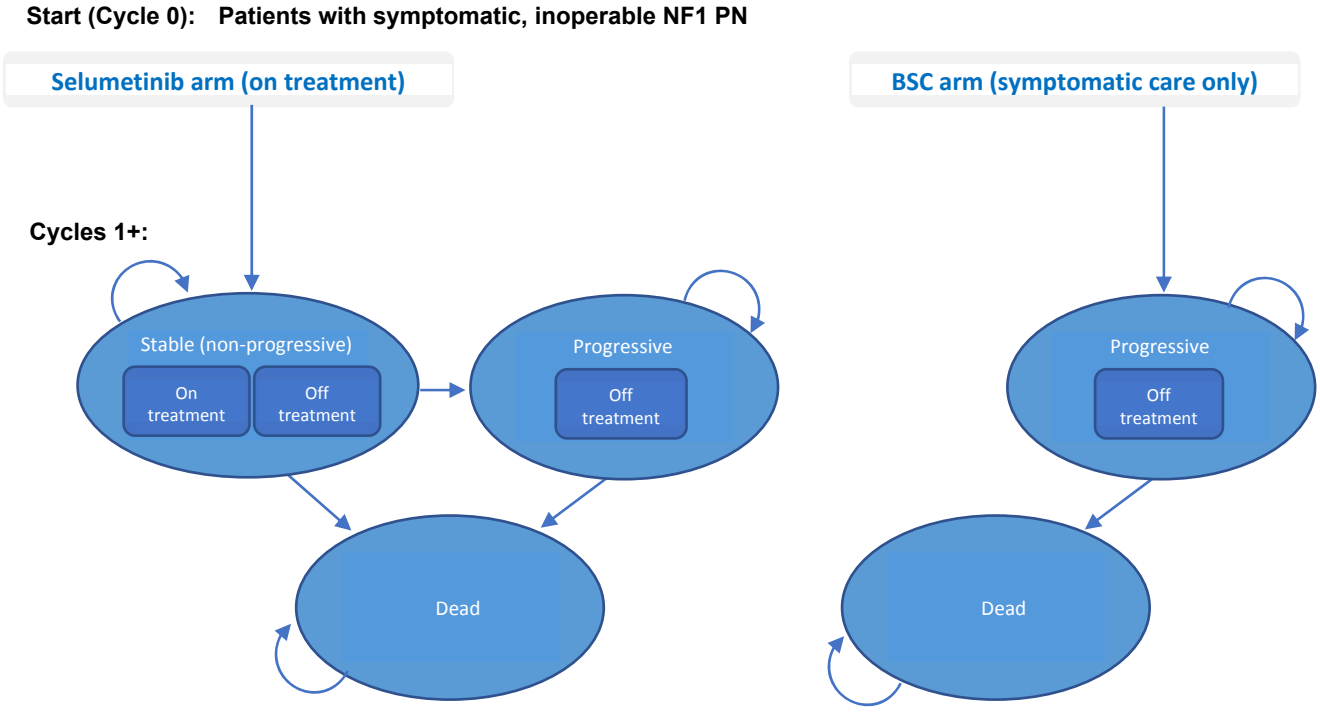
Selumetinib treatment results in durable reductions and stabilisation in tumour volume and PN growth, extended PFS, and improvements in HRQoL as demonstrated by the SPRINT study. Treatment with selumetinib stabilises or slows PN growth affecting PN volume; initiation of treatment in childhood targets the period where PN growth is most rapid. This is anticipated have a preventative effect that limits the future lifetime impact of PN, including the number and severity of morbidities, especially given that PN volume change tends to slow and plateau by the age of 16-18. Indeed, the PFS and TTD data from SPRINT demonstrate that there is residual benefit after discontinuing treatment, with patients very few progression events over the follow-up period. UK clinical experts validated and supported the rationale underlying the incorporation of potential preventative, durable and residual benefit after treatment discontinuation in the cost-effectiveness model.[28]

Patients in either arm were equally able to transition to the deceased state in each model cycle, based on general population mortality rates informed by UK life tables. An SMR was applied to account for a reduced life expectancy associated with NF1-related comorbidities (a PN-specific rate was not available from the literature), in order to accurately capture costs and benefits of the entire model time horizon.

The utility benefits accrued in the model were dependent on progression status (and adjusted for age-related disutilities). Progressive PN growth is associated with an increase in the number and severity of morbidities over time, resulting in a corresponding decrease in HRQoL.[1-3] Due to the progressive nature of NF1 PN, only patients receiving selumetinib can experience disease stabilisation or PN growth reduction in the model. The utility values associated with current clinical management and selumetinib are assumed to be interchangeable proxies for progressed and non-progressed health states, respectively (Section 10.6.1).

Treatment-related costs are accrued in the model when a patient is on selumetinib treatment in each one-year cycle. Patients in the selumetinib arm accrue treatment costs, AE costs and MRI costs based on TTD data from SPRINT, which are described in more detail in Section 12.2.1. Patients in the BSC arm accrue costs of current clinical management only, such as pain medication. Deceased patients accrued neither costs nor benefits.

Figure D2. Model schematic



12.1.4 Justify the chosen structure in line with the clinical pathway of care.

NF1 PN is a highly heterogeneous disease that can express differently between patients, and even within the same family with identical mutations.[29, 30, 100, 101] PN growth rates are most rapid in children with NF1 PN, with patients aged 3–5 years experiencing

unpredictable and uncontrolled PN growth at a median growth rate of 35% per year.[11] These high growth rates can ultimately result in very large tumour volumes and an increased risk in both the number and severity of morbidities, with a substantial negative impact on HRQoL.[11, 18, 19] As patients age, PN growth rates tend to slow and tumour volumes plateau into adulthood.[16, 17] Volume increases of ≥20% per year are rarely observed in adult patients,[16, 17] but patients will continue to experience the existing burden of PN-associated morbidities, resulting in poor HRQoL throughout their adult life with little hope of improvement.[11, 17, 19]

Taking into consideration the progressive natural history of NF1 PN, disease heterogeneity and limited data availability, a simplified AUC approach is the most appropriate structure for estimating the cost-effectiveness of selumetinib compared with current clinical management. This presents the most realistic and reliable analysis for patients with NF1 PN and reduces the number of additional assumptions that would otherwise be required by alternative model structures. Under these data constraints, it was not feasible to adequately represent NF1 PN in terms of mutually exclusive disease states (e.g. as part of a Markov state-transition model) or as a series of events (e.g. for a patient-level simulation).

Progressive PN growth can result in very large tumour volumes, which may generally be associated with an increase in the number and severity of morbidities over time, resulting in a corresponding decrease in HRQoL.[1-3] Feedback from clinical experts confirmed that, under the above constraints, **it is appropriate for the model to utility values that depend on whether a patient experiences progressive or stabilised PN growth**,[28] and that the trajectory of HRQoL in the model would generally reflect the experience of a 'typical' patient. This approach also allows for the potential lifetime benefit of limiting tumour growth and PN volumes in early childhood, where PN growth is most rapid, to be captured.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

An overview of all assumptions used in the cost-effectiveness model is provided in Table D3; the impact of individual assumptions on the results of the cost-effectiveness analysis is further explored as part of the sensitivity and scenario analyses (see Section 12.5).

Table D3. List of model assumptions

Assumption	Justification
Model population	
The SPRINT Phase II Stratum I trial population is representative of the UK population.	SPRINT Phase II Stratum I represents the best available evidence for the treatment of paediatric patients with symptomatic, inoperable NF1 PN with selumetinib; the trial further formed the basis of the marketing authorisation application for selumetinib in this indication. UK clinical experts confirmed that the baseline characteristics from SPRINT are generalisable to the relevant UK population.[28] The age of patients on model entry is based on the mean patient age in SPRINT Phase II Stratum I ([redacted] years), rounded to the next full integer for the purpose of the model.[18, 34] The gender split in the model is [redacted] males and [redacted] females, in line with SPRINT Phase II Stratum I.[18]

	The modelled BSA at entry is [redacted], in line with the mean BSA of the SPRINT Phase II Stratum I population.[34]
Model structure	
An AUC approach with simple occupancy of non-progressed, progressed or deceased states is sufficient to represent the disease course of NF1 PN. Utility accrued depends on progressive or stable PN growth status (and therefore also, indirectly, on treatment status).	Taking the heterogeneity of the disease and the limited data into consideration, a simplified approach was deemed most appropriate to model the disease course of NF1 PN and capture the HRQoL outcomes for patients with and without selumetinib (Section 12.1.3). This approach limits the number of additional assumptions that would be required, when compared with alternative model structures, and presents the most realistic case for patients with symptomatic inoperable NF1 PN.
Treatment-related costs are accrued according to time on treatment based on the SPRINT trial data.	Treatment-related costs are accrued according to whether the patient is on or off selumetinib treatment, which is based on TTD data from. All patients in the BSC arm receive an average cost associated with current clinical management of NF1 PN (e.g. pain medication).
Disease progression is modelled independently of treatment discontinuation.	Selumetinib results in durable reductions and stabilisation in tumour volume and PN growth, extended PFS, and improvements in HRQoL. Treatment with selumetinib in children with NF1 PN is anticipated to have an important preventative effect that limits the future lifetime impact of PN. The model accurately reflects the TTD and PFS data from SPRINT, which showed that patients tend to discontinue treatment at a faster rate than experiencing progressive PN growth. Although modelled independently, it is assumed that if patients have progressed, they are no longer on treatment (Markov-like approach). UK clinical experts validated and supported the rationale underlying the incorporation of potential preventative, durable and residual benefit after treatment discontinuation in the cost-effectiveness model.[28]
Model inputs	
In the selumetinib arm, all patients start on treatment and have stabilised disease within 1 year of initiation. Patients on BSC enter the model and remain in the progressed state until death.	The model reflects the disease course of NF1 PN, which is progressive in nature in the absence of disease-modifying treatment. Based on the SPRINT trial, patients receiving selumetinib see a rapid improvement with median time to initial response in SPRINT Phase II Stratum I less than one year (approximately [redacted] months).
Progression in the selumetinib arm is modelled using a simple annual probability derived from PFS data from SPRINT Phase II Stratum I.	Based on the SPRINT Phase II Stratum I data median PFS had not been reached and only 16% of patients had progressed by three years; see Section 9.6.[18] Therefore, a simple annual progression rate was derived from the cumulative probability of progression as the data were too immature for parametric analysis.
Treatment discontinuation in the selumetinib arm is based on parametric modelling of TTD data from SPRINT Phase II Stratum I.	Clinical trial data of selumetinib usage over time from the SPRINT Phase II Stratum I (based on patient-level data for TTD) represent the best available data for modelling time on treatment. Parametric analysis was conducted to extrapolate outcomes following the guidance outlined in NICE Decision Support Unit (DSU) Technical Support Documents 14 and 18.
Disease-related life expectancy is modelled according to an SMR for patients with NF1.	NF1 impacts patients' life expectancy (as described in Section 6). An NF1-specific SMR value of 2.02 is reported in the literature and was applied for the base case analysis.[165]
Overall survival is assumed equivalent across both arms, due to lack of data from the SPRINT	MPNSTs are thought to be associated with PN, with the risk of developing an MPNST being increased 20-fold in an area with an existing PN.[90] However, with a comparatively small study cohort and

study.	short follow-up duration, SPRINT Phase II Stratum I was not designed to evaluate the impact of selumetinib on mortality. As such, any potential impact of selumetinib is conservatively excluded from this analysis which assumes no incremental survival benefit.
The HRQoL of patients follows the disease course of NF1 PN and benefit associated with selumetinib; specifically: • Patients experiencing rapidly progressing PN have worse HRQoL than patients with stabilised disease • Upon discontinuation of selumetinib, the HRQoL effects of selumetinib diminish over the next 5 years	Rapid and uncontrolled PN volume growth in children can lead to very large tumour volumes and an increased risk in both the number and severity of morbidities, with a substantial negative impact on HRQoL The SPRINT study demonstrated that selumetinib results in durable improvements in HRQoL; in the model, this benefit persists until the patient progresses, even if the patient has discontinued treatment. Disease progression is assumed to result in a reduction in utility over a period of 5 years, back to the value of a paediatric patient without selumetinib. It should be noted that due to the preventative nature of initiating treatment with selumetinib and limiting PN growth in children, lifelong benefits are anticipated, as validated by several UK clinical experts;[28] this suggests the base case analysis is conservative.
The HRQoL of patients with progressive PN growth remains constant for the duration of the analysis	This is a simplifying, conservative assumption. In reality, longer periods of PN growth would be expected to result in very large tumour volumes and an increased risk in both the number and severity of morbidities, with a substantial negative impact on HRQoL over time (see Section 10.1.2 for a description of how patient HRQoL changes over time in the natural history of the disease). This suggests that the utility values in the BSC arm of the model may be slightly overestimated over time.
Pain and symptom medication constitutes the majority of BSC costs	One of the most common symptoms reported in NF1 PN is pain (see Section 6.1). It is assumed that selumetinib will be provided in addition to BSC, which is mostly for pain and symptom relief, as per SPRINT Phase II Stratum I data.[34] The Natural History study reported that during the observation period, 67.5% of PN required increasing pain medication.[11] As such, in the BSC arm, the estimated pain medication costs are increased by 67.5% compared to the selumetinib arm.
Adverse event costs	The cost of AEs associated with selumetinib are based on the most common Grade ≥3 AEs in SPRINT (see Section 12.2). Appropriate treatments have been selected based on local clinical guidance, and costs for these treatments were derived from the BNF, resulting in an average cost per patient of £2.85. It is conservatively assumed that this cost occurs in each year that a patient remains on treatment with selumetinib (i.e. that a patient experiences every type of event once in each year).
A carer disutility is applied to reflect the burden of NF1 PN on parents/carers	No utility data specific to parents/carers of NF1 patients were identified in the published domain. However, there is consensus from clinical experts that NF1 PN has a clear impact on the daily lives and QoL of families and carers, and this can be substantial. The analysis assumes that parents/carers experience the same relative HRQoL decrement as patients in the base case analysis. The relative mean difference in utility between the selumetinib and BSC patient cohort is applied as a weighting factor to the parent/carer utilities of those on BSC, to estimate the relative impact on HRQoL. Scenario analyses were conducted to assess the impact of different assumptions (see Section 12.5.16).

Abbreviations: AUC: area under the curve; BNF: British National Formulary; BSC: best supportive care; HRQoL: health-related quality of life; MPNST: malignant peripheral nerve sheet tumour; PFS: progression-free survival; PN: plexiform neurofibroma; TTD: time to discontinuation; SMR: standardised mortality ratio.

12.1.6 Define what the model's health states are intended to capture.

The simplified AUC approach considers three health states (stabilised or non-progressive disease, progressive disease and death), with the benefit of selumetinib being incorporated through the impact of stabilisation or reduction in PN volume growth on HRQoL.

As previously described, PN growth rates are most rapid in children with NF1 PN.[11] These high growth rates can ultimately result in very large tumour volumes and an increased risk in both the number and severity of morbidities, with a substantial, increasingly negative impact on HRQoL.[11, 18, 19] PN growth rates tend to slow, with tumour volumes plateauing by the age of 16-18,[16, 17] but patients will continue to experience the existing burden of PN-associated morbidities which have a lifelong impact on HRQoL.[11, 17, 19] Preventing or reducing the impact of NF1 PN during the most rapid stage of PN volume growth is likely to have a positive lifelong impact on patients.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table D4. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	100 years (lifetime horizon)	In line with the NICE reference case, this time horizon is sufficiently long to reflect all important differences in costs or benefits between the intervention and comparator over a patient's lifetime.	NICE Methods Guide[43]
Discount for costs and outcomes	3.5%	The same annual discounting rate of 3.5% was applied to costs and outcomes, in line with the NICE reference case.	NICE Methods Guide[43]
Perspective	UK NHS and PSS	In line with the NICE reference case, resource use and costs relevant to the NHS have been included.	NICE Methods Guide[43]
Cycle length	One year	Annual cycles provide sufficient granularity in order to capture the benefits of treatment with selumetinib over a lifetime horizon; half-cycle correction was applied.	N/A

Abbreviations: N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

Progression-free survival

The SPRINT trial demonstrated that selumetinib treatment results in durable reductions and stabilisations in tumour volume in children with symptomatic, inoperable NF1 PN (see Section 9.6 and 9.9 for further details). Children receiving selumetinib in the SPRINT trial had a higher probability of PFS over three years of follow-up compared with the Natural History study age-matched cohort (84% vs 15%). By inhibiting PN growth, selumetinib can prevent disease progression, extending PFS in patients with NF1 PN and improving patients' HRQoL. Tumour size reduction of any extent is rare under current clinical management, demonstrating the step-change in clinical outcomes provided by selumetinib.

To model the duration of patients experiencing stabilisation or reduction in PN growth, PFS was modelled by applying an annual probability of progression based on data from SPRINT Phase II Stratum I. **The observed cumulative probability of progression by three years on selumetinib (16%) was used to calculate an annual progression rate of 5.6%, applied for each one-year cycle throughout the time horizon** (Figure D4).[18] This method is appropriate because the majority of patients had not progressed by Year 3 of the SPRINT study, and the data were too immature to conduct parametric extrapolations for the purpose of the cost-effectiveness analysis.

PFS is modelled by applying a simple annual probability of progression based on PFS data from SPRINT Phase II Stratum I.

Time to discontinuation

Upon model entry, all patients within the selumetinib arm are assumed to be on treatment. Treatment discontinuation was implemented via parametric extrapolation of patient-level data of TTD from the SPRINT Phase II Stratum I. Parametric analyses of time-to-event data were conducted in line with the recommendations in NICE DSU TSD 14.[166] Six parametric distributions were explored to assess the most appropriate model for treatment duration (parameters and coefficients displayed in Table D4).

Table D4. TTD parameters

Distribution	Parameter	Coefficient
Exponential	Intercept	[redacted]
Generalised gamma	Mu	[redacted]
	Sigma	[redacted]
	Q	[redacted]
Gompertz	Shape	[redacted]
	Rate	[redacted]
Loglogistic	Shape	[redacted]
	Scale	[redacted]
Lognormal	Meanlog	[redacted]
	Sdlog	[redacted]
Weibull	Shape	[redacted]
	Scale	[redacted]

Footnotes: Parametric models were generated in R version 14 using the flexsurv package.
Abbreviations: TTD: time to discontinuation.

Selection of the most appropriate distribution was informed by goodness-of-fit statistics, visual inspection of the extrapolated curves against SPRINT Phase II Stratum I data, and clinical expert opinion. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) for each model are presented in Table D5, and the extrapolated curves (in addition to the TTD survival data from the SPRINT Phase II Stratum I) are visualised in Figure D3.

AIC and BIC statistics were very similar across all distributions, indicating that the parametric models fared similarly in terms of statistical fit. Therefore, selection was guided by clinical plausibility. Clinical expert opinion suggested that since tumour volume will stabilise as a patient reaches adulthood (see Section 6.1), discontinuation rates would likely be high.[28]

Although the exponential distribution had the lowest AIC and BIC values, it lacked clinical validity. **Clinical experts indicated that the Weibull distribution provided the most plausible predictions (which resulted in the highest rate of discontinuation over the 100-year time horizon).** The Weibull distribution was therefore applied for the base case analysis (Figure D3) with the remaining distributions tested in the scenario analysis (see Section 12.4).

Table D5. TTD goodness-of-fit statistics

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Abbreviations: AID: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to discontinuation.

Figure D3. TTD parametric models

Abbreviations: TTD: time to discontinuation.

Figure D4. Modelled PFS (annual probability) and TTD (Weibull) used in the base case

Abbreviations: PFS: progression-free survival; TTD: time to discontinuation.

NF1 PN patient utility

The utility values used in the cost-effectiveness analysis were derived from the TTO study (fully described in Section 10.4 to 10.6), as presented in Table C36. **The clinical rationale underlying modelled HRQoL was confirmed and validated by UK clinical experts**.[28] There was overall consensus that the following statements would generally hold true for a 'typical' patient with symptomatic inoperable NF1 PN:

- NF1 PN is a rare and lifelong disease that has a substantial impact on the HRQoL of patients across all domains of health, including: physical health, emotional wellbeing, and social development. In many cases, the disease results in an impaired ability to live a normal life (Section 7.1).[25, 26,28]
- With no active treatments currently available, clinical management comprises pain/symptom relief. As such, patients with symptomatic inoperable NF1 PN experience negatively impacted HRQoL compared with the general population (and NF1 population without PN).[28]
- Selumetinib treatment is expected to improve patients' HRQoL; in general, utility values would be higher with active treatment than for patients receiving only current clinical management.[28]
    - Some patients receiving selumetinib may experience reduced or stabilised PN growth; this would result in higher HRQoL value.
    - Some patients receiving selumetinib may still experience disease progression; this would have a negative impact on HRQoL as is currently seen under clinical management without selumetinib.

Parent/carer disutility

Given the burden of NF1 PN for parents/carer (see Section 7.1), the cost-effectiveness analysis incorporated a parent/carer utility decrement in the base case analysis. No direct quantitative evidence related to the HRQoL of parent/carer of children with NF1 PN was identified through the HRQoL SLR, and so the analysis assumes that parents/carer experience the same relative HRQoL decrement as patients (see Section 10.6).

According to the ONS, the average UK household size is 2.4 people, therefore the utility decrement was applied for 1.4 parents/carers, with the other person being the patient.[167]

Mortality

As discussed in Section 6.1, patients with NF1 have a higher mortality rate and lower life expectancy than the general population.[20-23] In addition, patients with NF1 PN have been shown to have a higher mortality rate than the general NF1 patient population.[165]

To incorporate disease-specific mortality in the model, general UK population life tables were used and adjusted by a SMR associated with NF1 PN, as sourced from the literature through a targeted literature search (Table D6). This approach accounted for the life expectancy of patients with NF1 PN in both the selumetinib and BSC arms.

The application of a single SMR to both arms in the model is conservative. Selumetinib is a disease modifying treatment and may have an impact on the mortality rate of patients with NF1 PN; but, due to data limitations it was not possible to incorporate this in the analysis.

Table D6. SMR used to adjust long-term mortality in both the selumetinib and BSC arms

SMR (95% CI)	Source
2.02 (1.6–2.6)	Duong et al. 2011[165]

Abbreviations: BSC: best supportive care; CI: confidence interval; SMR: standardised mortality rate.

Adverse events

The most commonly reported AEs of Grade ≥3 that occurred during SPRINT were diarrhoea ([redacted]), vomiting ([redacted]), pyrexia (fever) ([redacted]), hypoxia ([redacted]), paronychia (infection of the skin around fingernails and toenails) ([redacted]) and dermatitis acneiform (6%).[58] Most were of short duration (less than a week), except for paronychia which lasted for a mean duration of [redacted] and dermatitis acneiform which lasted for a mean duration of [redacted] (Table D7). For details on how corresponding costs have been calculated and incorporated into the model see Section 12.3.7.

Table D7. Adverse events reported in SPRINT and included in the economic analysis

Adverse event	Percentage of patients (n/N)	Mean duration, days (SD)
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Pyrexia (Fever)	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]

Abbreviations: SD: standard deviation.
Source: AstraZeneca Data on File (90DSU).[58]

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

To estimate the cost-effectiveness of selumetinib versus current clinical management, it was necessary to extrapolate treatment costs and clinical outcomes over lifetime horizon. As described in Section 12.2.1, PFS was extrapolated by applying an annual probability of progression based on data from SPRINT Phase II Stratum I; treatment duration was extrapolated and via parametric extrapolation of patient-level data of TTD, respectively. In line with the NICE reference case, HRQoL data was adjusted to patients' age at each time point in the model; established methodology by Ara and Brazier (2010) was used.[163]

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used and what other evidence is there to support it?

Not applicable.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

As detailed in Section 9.7, selumetinib monotherapy has a generally predictable and manageable safety profile in paediatric patients with NF1 PN, and AEs were usually mild or moderate in severity.[58] Adverse events are expected to have a minimal impact on HRQoL. The cost of Grade≥3 AEs was incorporated into the model for completeness, and the risk of each AE was based on data from SPRINT Phase II Stratum I (see Section 12.3).

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Clinical expert input was sought in order to validate the clinical rationale underlying various assumptions required in the economic analysis from a specific UK perspective. Full details are provided in Section 10.6.2.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

All clinical parameters and variables included in the cost-effectiveness analysis are summarised in Table D8.

Table D8. Summary of variables applied in the cost-effectiveness model base case

Variable	Value	Section(s) within document
Patient characteristics		
Mean age of patients (SD)	[redacted]	Section 12.1.1
Modelled starting age	[redacted]	
Proportion of males	[redacted]	
Mean BSA (SD)	[redacted]	
Model settings		
Discount rate: benefits	3.5%	Section 12.1.7
Discount rate: costs	3.5%	
Time horizon	100 years	

Half-cycle correction	Enabled	
Clinical inputs		
PFS extrapolation method	Simple probability of progression (5.6% annually)	Section 12.2.1
TTD extrapolation method	Weibull	
SMR for NF1 patients	2.02	
AE rates (selumetinib arm only)	Various, per event, according to SPRINT Phase II Stratum I data	
HRQoL inputs		
Paediatric patient without selumetinib	[redacted]	Section 10.6 Section 12.2.1
Paediatric patient with selumetinib	[redacted]	
Mean age of parent/carer at childbirth	30.6	
Number of carers per patient	1.4	
Cost inputs		
Cost of selumetinib per pack (list price)	£4,223.59 (10 mg pack)* £10,560.00 (25 mg pack)*	Section 12.3.3
Selumetinib pack size	60 capsules	
Total treatment-related AE costs (selumetinib arm; patients on treatment only)	£[redacted] per patient per year	Section 12.3.7
Pain medication costs	£[redacted] per year (selumetinib arm) £[redacted] per year (BSC arm)	Section 12.3.6
Resource use (MRI) costs (selumetinib arm only)	£264.50 per MRI examination	Section 12.3.5

Abbreviations: BSA: body surface area; HRQoL: health related quality of life; MRI: magnetic resonance imaging; NF1: neurofibromatosis type 1; PAS: patient access scheme; PFS: progression free survival; SD: standard deviation; SMR: standardised mortality rate; TTD: time to discontinuation.
* A confidential PAS of [redacted] is included in the economic analysis.

12.3 Resource identification, measurement and valuation

Resource identification, measurement and valuation studies

12.3.1 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

An SLR was conducted in January to February 2021, in order to identify all relevant published literature on HRQoL, cost and resource use, and economic evaluations in patients with NF1, as well as that of their family and carers. The methodology and results of the cost and resource use searches are outlined in Section 11 and the Appendix (Section 17.6).

In total four publications were identified reporting on four unique studies. An overview of the studies reporting cost and resource use data is provided in Table D9, with a more detailed table of the extracted information for all four studies provided in the Appendix (Section 17.6.9).

Table D9. Overview of cost and resource use studies included in the economic SLR

Source	Study design and patient population	Country and cost year	Valuation methods and information reported
Rosser 2018[155]	NF1 patients with symptomatic and inoperable PN, aged >16 years.	US Cost year not reported.	Trial methodology not reported. Patients enrolled in the trials completed a background information form, including pain and other medications, at baseline. No additional data sources were given.
Widemann 2014 (NCT00021541)[41]	Phase II randomised, flexible crossover, double-blinded, placebo-controlled trial. Children and young adults ≥3 and ≤25 years with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity, meeting the eligibility criteria were included. Patients who underwent prior surgery for their progressive PN were eligible provided the residual tumour was measurable.	US Cost year not reported.	Participants' prior medical treatment for their PN was recorded at baseline for 60 participants. No additional data sources were given.
Wolters 2015[19]	Analysis of patients enrolled on a natural history protocol at NCI. Patients included in the study were children and adolescents six to 18 years of age with NF1 PN. Eligibility criteria included diagnosis of NF1 according to the NIH Consensus Conference criteria or a confirmed NF1 germline mutation with analysis performed in a CLIA-certified laboratory.	US Cost year not reported.	The proportion of patients taking pain medication, and the medication type were reported by parents at the start of the study.
Yang 2020[168]	Patients included in this study were diagnosed with both NF1 and PN, aged ≤18 on the index date, and continuously enrolled for ≥12 months before the index date. Continuous enrolment was defined as no lapse in insurance coverage longer than 45 days.	US The cost data were collected from October 2014 to March 2018. All costs	Patient data were collected from MarketScan® CCAE database. Patient data were collected from the baseline, index and follow-up periods. The index date was the date of first diagnosis of NF1 or PN, whichever occurred later, on or after October 1, 2015. The baseline period was defined as the 12-month period before the index date.

Source	Study design and patient population	Country and cost year	Valuation methods and information reported
		were adjusted to 2018 US dollars based on the medical care component of the Consumer Price Index.	The follow-up period varied in length, spanning from the index date to the end of the study period or the end of continuous enrolment in the health plan, whichever occurred first. All-cause healthcare resource utilization included medical costs (inpatient, outpatient, ER and other encounters) and pharmacy costs. Treatments were broadly classified as surgery for PN, pain medication, chemotherapy, radiotherapy, and targeted therapies. Claims for imaging services (CT, MRI and PET) were identified by the Healthcare Common Procedure Coding System and ICD PROC codes. Healthcare costs PPPY were calculated as the total cost divided by the total number of days of enrolment in years, where costs were weighted by each patient's length of follow-up to avoid overestimation and annualised for patients observed <1 year.

Abbreviations: ALT: alanine transferase; ANC: absolute neutrophil count; CCAE: Commercial Claims and Encounters; CRU: cost and resource use; CT: computed tomography; CLIA: Clinical Laboratory Improvement Amendments; ECOG: Eastern Cooperative Oncology Group; ER: emergency room; Hb: haemoglobin; HRQoL: health related quality of life; ICD PROC, International Classification of Diseases Procedure Coding System; IPI: International Prognostic Index; LQ: lower quartile; MRI: magnetic resonance imaging; NCI: National Cancer Institute; NF1: neurofibromatosis 1; NHS: National Health Service; NR: not reported; NRS-11: 11-Item Numerical Rating Scale; NSAIDs: nonsteroidal anti-inflammatory drugs; OTC: over the counter; PET: positron emission imagine; PNs: plexiform neurofibromas; PPPY: per patient per year; QoL: quality of life; SD: standard deviation; SLR: systematic literature review; SSRI: selective serotonin reuptake inhibitor; ULN: upper limit of normal; US: United States of America; UQ: upper quartile

12.3.2 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

Clinical expert input was sought in order to validate the clinical rationale underlying various assumptions required in the economic analysis from a specific UK perspective. Full details are provided in Section 10.6.2.

Technology and comparators' costs

12.3.3 Provide the list price for the technology.

Selumetinib is provided as 10 mg capsules in a pack size of 60 capsules at a list price of £4,223.59, and as 25 mg capsules in a pack size of 60 capsules at a list price of £10,560.00.

12.3.4 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

A simple patient access scheme (PAS) discount of [redacted] has been submitted to NICE PAS Liaison Unit (PASLU), resulting in a discounted net price of £[redacted] for a pack of 10 mg capsules (60x) and £[redacted] for a pack of 25 mg capsules (60x). Unless specified otherwise, the price including confidential PAS has been used in the cost-effectiveness analysis throughout this submission document.

12.3.5 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Costs associated with selumetinib

During the pivotal SPRINT Phase II Stratum I, selumetinib was administered according to body surface area (BSA)-based dosing, with doses rounded to the nearest 5–10 mg using a dosing nomogram (Table D10).[38, 40] Selumetinib is administered at a dose of 25 mg/m^2 BSA, twice daily (approximately every 12 hours), up to a maximum single dose of 50 mg.[37]

Table D10. Dosing nomogram from SPRINT

BSA (m^2)	0.55–0.69	0.70–0.89	0.90–1.09	1.10–1.29	1.30–1.49	1.50–1.69	1.70–1.89	1.90–2.04
Dose required (25 mg/m^2/dose)	20 (morning) 10 (evening)	20	25	30	35	40	45	50
Capsules required to deliver dose								
10 mg	1.5	2	-	3	1	4	2	-
25 mg	-	-	1	-	1	-	1	2
Cost per dose[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Also taking into consideration the cost-per-capsule as detailed in Section 12.3.4
Abbreviations: BSA: body surface area.

Using the cost-per-dose data presented in Table D10, the annual cost per annum for patients with differing BSA can be calculated, as presented in Table D11.

Table D11. Costs-per-patient associated with selumetinib

BSA (m^2)	Dose (mg)	Cost/dose	Cost/day	Cost/annum
0.55–0.69	20 (morning) 10 (evening)	[redacted]	[redacted]	[redacted]
0.70–0.89	20	[redacted]	[redacted]	[redacted]
0.90–1.09	25	[redacted]	[redacted]	[redacted]
1.10–1.29	30	[redacted]	[redacted]	[redacted]
1.30–1.49	35	[redacted]	[redacted]	[redacted]
1.50–1.69	40	[redacted]	[redacted]	[redacted]
1.70–1.89	45	[redacted]	[redacted]	[redacted]
1.90–1.94	50	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area.

In the base case analysis, patients enter the model with a mean BSA of [redacted] aligned with the SPRINT cohort (see Section 12.1.1). To provide an accurate estimate of selumetinib dose required per patient, BSA was assumed to increase annually according to a linear regression algorithm that estimates BSA based on age and gender split. The parameters used for the linear regression are presented in Table D12; the linear regression results plotted against the observed SPRINT data is presented in Figure D5. BSA is assumed to stabilise from the age of 18, when patients are also assumed to discontinue treatment. For further details regarding treatment duration, please see Section 10.7 and 12.2.1.

Table D12. BSA linear regression parameters

Parameter	Value
Age	[redacted]
Constant	[redacted]

Abbreviations: BSA: body surface area.

Figure D5. Fit of linear regression to BSA data over time from SPRINT

Abbreviations: BSA: body surface area.

The most frequently used pain medications during SPRINT were paracetamol ([redacted]%), ibuprofen ([redacted]%) and gabapentin ([redacted]%).[34] The analysis crudely assumes these treatments are required annually. The cost applied to the selumetinib arm also includes costs for; naproxen, pregabalin, lidocaine, oxycodone, hydromorphone, morphine, diazepam, celecoxib, ketamine, lidocaine, methadone, tramadol, amitriptyline, diazepam and ibuprofen. These medications were used in less than 10% of the cohort but are included for completeness, resulting in an overall average cost of pain medication for patients receiving selumetinib of £[redacted] per annum. Costs were sourced from the British National Formulary (BNF).

Costs associated with current clinical management (BSC)

Current clinical management of NF1 PN relies on pain and symptom relief. Pain is one of the most frequently reported symptoms of NF1 patients with symptomatic PN and as such, for completeness, the analysis includes the associated pain medication costs. Gross et al. 2018 reported that during the observation period, 67.5% PN required increasing pain medication.[11] As such, in the BSC arm the estimated pain medication costs are increased by [redacted]% to £[redacted] per annum.

Health-state costs

12.3.6 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a

rationale for the choice of values used in the cost- effectiveness model.

Based on clinical expert feedback, NF1 patients with symptomatic, inoperable PN are assessed frequently by HCPs throughout each year. It is not anticipated that additional test or investigations for the identification of NF1 patients with symptomatic, inoperable PN (i.e. patients eligible for treatment with selumetinib), beyond those already used in current clinical practice, will be required. However, for completeness, the model assumes that up to two additional MRI scans may be required for monitoring patients when on selumetinib treatment on an annual basis (with an assumed cost of £264.50 per MRI examination, based on 2018–19 NHS reference costs [RD07Z]).

There are no additional health state costs other than those outlined above and in Section 12.3.5.

Adverse-event costs

12.3.7 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The cost of AEs associated with selumetinib are based on the most common Grade ≥3 AEs in SPRINT (see Section 12.2). Appropriate treatments have been selected based on local clinical feedback, and costs for these treatments were derived from the BNF. Table D13 shows the estimated cost of treating the listed adverse events, resulting in a weighted average cost per patient of £[redacted]. It is conservatively assumed that this cost occurs in each year that a patient remains on treatment with selumetinib (i.e. that a patient experiences these AEs once in each year).

Table D13. Cost of adverse events with selumetinib

Adverse event	Treatment	Estimated cost per event	Proportion of patients experience AE
Diarrhoea	Loperamide (Various doses – assumed a single pack would resolve symptoms. 2mg, 30 tablets at £1.58 per pack)	£1.84	[redacted]
Vomiting	Ondansetron (4mg, two times per day for up to 5 days– 10 tablets at £1.07 per pack)	£1.07	[redacted]
Pyrexia (Fever)	N/A	N/A	[redacted]
Hypoxia	N/A	N/A	[redacted]
Paronychia	Flucloxacillin (250mg four times a day for 7 days – 28 caps at £1.72 per pack)	£37.71	[redacted]
Dermatitis acneiform	Metronidazole cream (Typical duration of symptoms was 4 months, assume one 40mg unit would be sufficient for 1 month treatment. 40g of, 7.5mg metronidazole per gram, at £9.88 per unit)	£3.44	[redacted]
Weighted average cost of adverse events per patient		**£[redacted]**	

Abbreviations: N/A: not applicable.
Source: BNF[169]; AstraZeneca Data on File (90DSU).[58]

Miscellaneous costs

12.3.8 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Not applicable.

12.3.9 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Through qualitative evidence, and feedback and discussions with UK clinical experts consulted for this submission, it is clear that **a range of support services are currently required for patients with NF1 PN, as well as their parents and carers**.[28] Although it has not been possible to quantify additional support required or potential resource savings, due to general lack of data and/or inability to quantify the impact due to the heterogeneity of NF1 PN, **resource savings throughout the wider UK government bodies are possible if there is a reduction in the need for other forms of care such as those described below**:

- **Educational and schooling support**

Although it depends on a case-by-case basis, a high percentage of learning difficulties associated with NF1, independent of PN. This may be especially true for patients whose PN are affecting their vision or general comfort levels that can affect learning.

- **Physiotherapy and occupational therapy**

  PN can affect motor skills, particularly with those commonly located near the limbs, joints or neck; the patient may need to be assessed for additional physical or functional needs. Occupational therapy is an important consideration, as patients may require special considerations including wheelchair provision, seating adjustments, and functionality support such as using hands.

- **Psychological support**

  There was clear consensus across the UK clinical experts that dedicated support can be key for patients as well as parents, throughout their lifetime. The need for psychological support is indicated through the presence of a Consultant Child Psychiatrist within the multi-disciplinary team managing NF1 PN patients in the specialist centre in Manchester (see Section 8 for further details)[59] and offers services through an additional psychology team.

Finally, owing to the preventative nature of initiating treatment with selumetinib and limiting PN growth in children, lifelong benefits are anticipated that can extend throughout their adult lives. Clinical experts noted that NF1 PN can negatively influence career prospects and job choices throughout life, due to the physical ad functioning impairments associated with PN.[28] Selumetinib can open opportunities that may not otherwise have been possible. In terms of the wider societal benefits, this may result in productivity gains for patients, parents and carers more broadly.

12.4 Approach to sensitivity analysis

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

The uncertainty around the model parameters (as outlined in Table D40) has been explored in deterministic and probabilistic sensitivity analyses, further details of which can be found in Section 12.4.2. This section describes the scenario analyses.

Scenario analyses

An extensive list of scenarios explored to understand the impact of uncertainty around model assumptions (

Table D14). The results of all scenario analyses are discussed in Section 12.5.16.

Table D14. Scenario analyses to test uncertainty

Structural assumption	Base case	Scenario(s)	Rationale
Starting age at entry	[redacted]	Alternative age ranges*: • 5 years • 15 years	Test the impact of assuming different starting age for initiating treatment with selumetinib.
Parametric models for TTD	Weibull	Alternative parametric models: • Exponential • Generalised gamma • Gompertz • Loglogistic • Lognormal	Explore the impact of alternative parametric models fitted to the patient-level TTD data from SPRINT.
Discounting	3.5%	1.5%	Cost-effectiveness analyses with long time horizons can be heavily impacted by discount rates. Per HST draft guidance (2017), a discount rate of 1.5% for costs and benefits may be considered if it is highly likely that long-term health benefits are likely to be achieved.[170]
Treatment-related costs for selumetinib (AEs, MRI scans)	Included	Excluded	Test the impact of additional AE and MRI costs on the results.
Exclusion of SMR	Included	Excluded	Understand the impact of applying different assumptions for mortality associated with NF1 PN and with selumetinib versus current clinical management.
Differential SMR	2.02	A 5% improvement in SMR associated with selumetinib: • 1.92 for the selumetinib arm • 2.02 for the BSC arm	
Parent and carer utility (relative difference)	100%	Alternative relative impact assumed: • 75% • 50%	Explore the impact of different methods for incorporating the parent and carer HRQoL burden associated with NF1 PN in the cost-effectiveness analysis.
Duration of carer impact	Until patient reaches 18 years of age	Alternative durations: • Until patient reaches 24 years of age • Until carer reaches 64 years of age • For the duration of carer lifetime	
Decrement in carer utility	Parents/carers experience the same relative	Absolute reduction of −0.08 per carer (HST 11)	

	HRQoL decrement as patients		
Years to achieve treated HRQoL after initiating treatment	All patients start with the utility of an untreated patient ([redacted]) and this increases to the utility value of a treated patients ([redacted]) over 1 year	All patients start with the utility of an untreated patient ([redacted]) and this increases to the utility value of a treated patients ([redacted]) over either 2 or 3 years	Explore the impact of different assumptions regarding the HRQoL benefits associated with selumetinib in the economic model (how quickly patients experience the HRQoL benefit from the start of treatment; and the duration of sustained benefits after treatment discontinuation).
Years to revert to baseline HRQoL after discontinuing treatment	For patients who progress before 18 years of age, utility decreases from that of a treated patient ([redacted]) to that of an untreated patient ([redacted]) over a 5-year period	For patients who progress before 18 years of age, utility decreases from that of a treated patient ([redacted]) to that of an untreated patient ([redacted]) over a 2- or 8-year period	

Abbreviations: AE: adverse event: HRQoL: health-related quality of life; MRI: magnetic resonance imaging; SMR: standardised mortality ratio; TTD: time to discontinuation.
* BSA at model entry adjusted accordingly to match the starting ages in the scenario; the starting age may also have different implications for the maximum duration of treatment which is also adjusted accordingly to thirteen and three years, in the scenarios.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (DSA) were conducted by varying the input for all parameters in the model, whilst keeping all other inputs the same. For certain parameters where estimates of precision were available, the lower and upper limits were defined by the 95% CI around the mean. If no measure of uncertainty was available the parameter was varied by ±20% of their base case mean value. All inputs included in the DSA, together with the corresponding upper and lower values, are presented in Section 12.4.3.

The ICER was recorded for each upper and lower value, and the ten parameters with the highest impact on the ICER were used to produce a tornado diagram displaying the results of the DSA (see Section 12.5.11).

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were conducted to assess the combined parameter uncertainty on the results of the cost-effectiveness analysis through repeated random, simultaneous variation of selected input parameters. Variation of included parameters was performed on the basis of the base case mean value and corresponding standard deviation, where available, as well as the appropriate probability distribution for each parameter. If the standard deviation was not available, a proxy was calculated as follows (with the NORMSINV function returning the inverse of the standard normal cumulative distribution in Microsoft Excel):

$$(Upper\ range - Lower\ range)/(2 * NORMSINV(0.975))$$

The upper and lower range were based on the CI, where available, or otherwise determined via ±20% variation around the mean value.

A total of 10,000 individual simulations were recorded and the results, in the form of incremental costs and benefits, plotted on a cost-effectiveness plane (see Section 12.5.13).

A list of the parameters and their corresponding probability distributions in the PSA are presented in Section 12.4.3.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table D15. Variables used in the sensitivity analysis

Variable	Base-case value	Range of values	Distribution
Proportion of cohort that are male	[redacted]	[redacted]	Beta
Average age at entry	[redacted]	[redacted]	Gamma
BSA at entry	[redacted]	[redacted]	Gamma
NF1 SMR	2.02	1.6–2.6	Gamma
Weibull: shape parameter	[redacted]	[redacted]	Cholesky
Weibull: scale parameter	[redacted]	[redacted]	Cholesky
Utility: with selumetinib	[redacted]	[redacted]	Beta
Utility: without selumetinib	[redacted]	[redacted]	Beta
Utility: age adjustment constant	0.951	0.761–1.141	Gamma
Utility: age adjustment male coefficient	0.021	0.017–0.025	Beta
Utility: age adjustment age coefficient	-0.00026	-0.00021 – -0.00031	Normal
Utility: age adjustment age^2 coefficient	-0.00003	-0.000027 – -0.000040	Normal
Discount rate: outcomes	3.50%	1.50–6.00%	NA
Discount rate: costs	3.50%	1.50–6.00%	NA

Cumulative probability of progression by Year 3	16.00%	5.84–26.16%	Beta
BSA: linear regression constant	[redacted]	[redacted]	Beta
BSA: linear regression coefficient for age	[redacted]	[redacted]	Beta
Number of carers	1.4	0–2	Gamma
Parents age at birth of patient	30.6	20–40	Gamma
Years to revert to untreated HRQoL	5	2–8	Gamma
Cost of MRI	£265	£60–£301	Gamma
Annual number of MRIs for selumetinib patients	2	0–4	Gamma
Cost of managing selumetinib AEs	[redacted]	[redacted]	Gamma
Cost of pain medication for patients receiving selumetinib	[redacted]	[redacted]	Gamma
Increase in pain medication for those on BSC	[redacted]	54–81%	Beta

Abbreviations: AE: adverse event; BSA: body surface area; BSC: best supportive care; HRQoL: health-related quality of life; MRI: magnetic resonance imaging; NF1: neurofibromatosis 1; SMR: standardised mortality ratio.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

The acquisition drug cost and dosing nomogram for selumetinib was not included, as these inputs are not subject to uncertainty. However, BSA (and associated parameters) were varied.

All other parameters were included in the sensitivity analysis.

12.5 Results of economic analysis

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

As shown in Table D16, the base case analysis (using the PAS price for selumetinib) resulted in an ICER for selumetinib of £93,169 per QALY gained. Selumetinib therefore represents a cost-effective use of NHS resources when considered at the PAS price, with an ICER below the £100,000 per QALY willingness-to-pay threshold. Selumetinib is expected to provide an additional [redacted] QALYs versus current clinical management, which is consistent with the benefit of associated lifelong impact of preventing PN growth from childhood, where PN volume growth has been observed to be most rapid. These benefits are associated with an incremental cost of [redacted].

Table D16. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,169

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Selumetinib treatment results in reductions in tumour volume, reduced or stabilised PN growth rates, extended PFS, which leads to improvements in HRQoL for patients with symptomatic, inoperable NF1 PN.

Due to the limited data availability and disease heterogeneity associated with NF1 PN, the specific outcome measures reported from the clinical trial are not explicitly modelled. The utility data from the TTO study and modelled outcomes for HRQoL (i.e., QALYs gained) are more relevant, as these reflect the anticipated HRQoL improvement with selumetinib. These results are presented in Section 12.5.1 above.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Not applicable; health state occupancy over time are available for viewing in the economic model.

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The underlying clinical rationale behind health state utility values and the inputs used in the model are detailed in Section 10 and Section 12.2. Plots of QALYs accrued over time with selumetinib and BSC are presented in Figure D6 and Figure D7, respectively.

Figure D6. Selumetinib QALYs accrued over model time horizon

Abbreviations: QALYs: quality-adjusted life years.

Figure D7. BSC QALYs accrued over model time horizon

Abbreviations: BSC: best supportive care; QALYs: quality-adjusted life years.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Not applicable.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Not applicable.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table D17. Undiscounted base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

A breakdown of the costs for both selumetinib and BSC is provided in Table D18.

Table D18. Undiscounted base case results

Item	Cost selumetinib	Cost BSC	Increment	Absolute increment	% Absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost (MRI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain medication cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BSC: best supportive care; MRI: magnetic resonance imaging.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Not applicable.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Figure D8 and Table D19 present the results of the one-way sensitivity analysis for selumetinib versus BSC, indicating the ten parameters with the greatest impact on the ICER.

Figure D8. Results of one-way deterministic sensitivity analysis

Abbreviations: BSA: body surface area.

Table D19. Results of one-way deterministic sensitivity analysis (ten most influential parameters)

Variable (lower bound to upper bound)	ICER with lower bound	ICER with upper bound
Weibull: scale (to ; base case)		
Utility - Untreated (to ; base case)		
Discount rate outcomes (1.50% to 6.00%; base case 3.50%)		
No. of carers (0.00 to 2.00; base case 1.40)		
Utility Age Reg constant (0.761 to 1.141; base case 0.951)		

Cumulative probability of progression (5.84% to 26.16%; base case 16.00%)	[redacted]	[redacted]
Utility - Treated ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]
BSA ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]
Discount rate costs (1.50% to 6.00%; base case 3.50%)	[redacted]	[redacted]
BSA Linear regression age coefficient ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]

Abbreviations: BSA: body surface area; ICER: incremental cost-effectiveness ratio.

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Not applicable.

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Table D20. PSA results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Average ICER (£/QALY)
BSC, mean (95% CI)	[redacted]	[redacted]	-	-	-
Selumetinib, mean (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

Figure D9 and Figure D10 present the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC), respectively. Across 10,000 PSA simulations, selumetinib was associated with mean incremental cost of [redacted] (95% CI: [redacted]) and mean incremental QALYs of [redacted] (95% CI: [redacted]; 95% CIs were calculated based on the 2.5 and 97.5 percentiles of these simulations) resulting in an average ICER of [redacted] per QALY (Table D20). The results are highly consistent with the deterministic cost of [redacted] and a deterministic increase in QALYs of [redacted], which gives a base-case ICER of £93,169 per QALY.

Figure D9. Cost-effectiveness plane

Abbreviations: QALY: quality-adjusted life-year.

Figure D10. Cost-effectiveness acceptability curve

Abbreviations: BSC: best supportive care.

12.5.14 What were the main findings of each of the sensitivity analyses?

Deterministic sensitivity analysis

As is expected for this analysis, where there are a limited number of key input parameters, the model was most sensitive to variations in inputs related to accruing cost and HRQoL outcomes, including:

- Treatment duration parameters
- Utility values associated with stabilised disease and progressive disease
- Discount rates for both outcomes and costs
- Parent and carer HRQoL assumptions
- Probability of progression

Probabilistic sensitivity analysis

Across 10,000 PSA simulations, the average ICER of [redacted] per QALY (Table D20) was highly consistent with the base-case ICER of £93,169 per QALY, demonstrating good robustness to uncertainty around the input parameter estimates.

12.5.15 What are the key drivers of the cost results?

Please see responses above.

Miscellaneous results (scenario analysis)

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

A wide range of scenario analyses were undertaken as it was important to explore the impact of varying the model assumptions from the base case analysis. These were outlined in Section 12.4.1, with the results of the analyses provided below.

Starting age at entry

Age is used to estimate starting BSA which is directly used to calculate the cost of selumetinib in the model. UK clinical experts supported the base case analysis using the average starting age of [redacted] years in the SPRINT study:[28]

- The SPRINT data were deemed generalisable to the UK setting
- Clinical experts confirmed that starting treatment very early is unlikely to occur in clinical practice due to multiple practical reasons, including the likely inability to swallow capsules at a young age (<7 years), the time needed for PN to develop to become symptomatic (and to be deemed inoperable)

- One clinical expert suggested the reasons above could lead to the starting age being above 10 years of age (perhaps in early adolescence)

However selumetinib is indicated in paediatric patients with symptomatic inoperable NF1 PN, who may start treatment from as young as 3 years old, and it is unclear what the average age of treatment initiation would be in clinical practice, therefore, age was varied in the scenario analyses. The results of this scenario are presented in Table D21, which demonstrate an improvement in the ICERs from the base case analysis.

Table D21. Scenario analysis – age at baseline

Starting age (years)	Incremental costs (£)	Incremental QALYs	ICER
5	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Alternative parametric distributions for TTD

Following NICE DSU TSD 14, several parametric distributions for the TTD data were explored. Similar AIC and BIC values were found across all distributions, suggesting that there is no major difference between them. Whilst the Weibull distribution was the most clinically appropriate curve, for completeness the results using the other alternative parametric distributions are presented in Table D22.

Table D22. Scenario analysis – time to discontinuation parametric distributions

TTD parametric distribution	Incremental costs (£)	Incremental QALYs	ICER
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	£93,169

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TTD: time to discontinuation.

Alternative discount rates

The NICE Guide to the Methods of Technology Appraisal state that a non-reference case discount rate of 1.5% for costs and outcomes may be considered if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved.[43]

Within this cohort, the HRQoL benefits are likely to persist for the patients' lifetime following discontinuation as PN progression slows or halts in adulthood. As such, the incremental benefit realised with selumetinib will persist for the long term. It is therefore appropriate to consider the impact of this alternative discount rate of 1.5% for both costs and outcomes (Table D23), which demonstrates a substantial improvement in the results.

Table D23. Scenario analysis – alternative discount rate

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Excluding treatment-related costs for selumetinib (AEs, MRI scans)

Table D24 presents the results of the scenario analysis where additional treatment-related costs of AEs and MRIs associated with selumetinib are excluded.

Table D24. Scenario analysis – excluding treatment-related costs for selumetinib

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Exclusion of SMR

The scenario results demonstrate that excluding the SMR rate associated with NF1 had minimal impact on the results.

Table D25. Scenario analysis – exclusion of SMR

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year; SMR: standardised mortality ratio.

Differential SMR

With a lifetime horizon, and the potential benefit of selumetinib on patient mortality may be an important factor to consider as reduced and stabilised PN volume may correspondingly reduce the risk of malignancies such as MPNSTs. This was not included in the base case analysis due to lack of data on mortality from the SPRINT study; therefore, in the scenarios, an arbitrary improvement of 5% is tested, resulting in an SMR of 1.92 compared to the baseline rate of 2.02 for those on BSC. With this nominal change there was minimal, almost neglible impact on the results (Table D26).

Table D26. Scenario analysis – differential SMR

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year; SMR: standardised mortality ratio.

Parent/carer utility (relative difference)

The following analyes consider the impact of different assumptions of parent and carer HRQoL in the economic model, including the size of impact relative to the benefit experienced by the patient, the duration of burden on parents and carers, and testing an alternative approach using a single disutility value obtained from a previous HST submission.

Table D27. Parent/carer utility – relative difference set to 75%

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D28. Parent/carer utility – relative difference set to 50%

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D29. Parent/carer utility – impact persists until the patient reaches 24 years of age

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D30. Parent/carer utility – impact persists until the parent/carer reaches

64 years of age

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D31. Parent/carer utility – impact persists for the duration of parent/carer lifetime

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D32. Parent/carer utility – absolute utility decrement of 0.08 in BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Alternative assumptions on utility change over time

The base case analysis assumes that all patients start with the utility of an untreated patient ([redacted]) and that for those patients receiving selumetinib the utility increases to that of a treated patient ([redacted]) over the first year. Scenarios have been explored to understand the impact of different assumptions regarding the HRQoL benefits associated with selumetinib in the economic model, by varying:

- How quickly patients experience the HRQoL benefit from the start of treatment; and
- The duration of sustained benefits after treatment discontinuation.

Given the data from SPRINT that demonstrates a rapid improvement in HRQoL after initiating treatment, durable response and improvements in clinical outcomes, and the clinical rationale underlying the lifelong benefit of preventing and limiting the impact of PN in childhood, these scenarios are deemed to be conservative. Nonetheless, the results

below are robust to the HRQoL assumptions implemented in the model (Table D33 to Table D36).

Table D33. Years to achieve treated HRQoL after initiating treatment (2 years)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D34. Years to achieve treated HRQoL after initiating treatment (3 years)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D35. Years to revert to baseline HRQoL after discontinuing treatment (2 years)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table D36. Years to revert to baseline HRQoL after discontinuing treatment (8 years)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

12.6 Subgroup analysis

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Due to the degree of heterogeneity within the relevant NF1 PN patient population, it was not feasible to conduct subgroup analyses.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effective ness analysis.

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

For quality assurance, a senior health economic modeller that was not involved in the model development, performed quality assurance. This entailed:

- Review of modelling structural assumption and techniques chosen
- Review of technical deployment (formulas, functionality)
- Review of data inputs and sources
- Conducting extreme scenario analyses and validation of results

In addition, all key clinical model inputs and concepts, and relevant model assumptions were validated with clinical experts in NF1 PN during a series of one-to-one interviews, which are described in more detail in Section 10.6.2.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

As detailed in Section 11, an SLR of economic evidence for patients with NF1 was not able to identify any published economic evaluations relevant to the decision problem covered in this submission.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness analysis was performed in line with the population for whom selumetinib is indicated, and the decision problem addressed in this submission (i.e. all paediatric patients with NF1 and symptomatic, inoperable PN). The analysis thus covers all patients eligible for treatment with selumetinib in England.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

NF1 PN is a rare and highly heterogeneous disease that can present very differently between patients, both in the physical presentation and the associated symptomatology. **If reimbursed in the UK, selumetinib will be the first active treatment available resulting in a step-change in the disease management for this patient population, where the disease burden is high for both paediatric patients with symptomatic inoperable NF1 PN, as well as their parents and families.**

To our knowledge, **this submission presents the first cost-effectiveness analysis for patients with NF1 PN**. Due to limited availability of data, model structures such as full Markov state-transition and patient-level simulation models that are used across other disease areas were unfeasible, and a simplified AUC model structure was required. The model developed for this submission reflects the disease impact of NF1 PN on HRQoL, and considers the potential lifetime benefit associated with selumetinib through reducing and stabilising tumour volume and PN growth, extended PFS, and improving patients' quality of life. Additionally, to address the evidence gaps around utility values, we conducted a novel TTO study specifically aimed at eliciting appropriate utility values in NF1 PN. Where necessary, conservative assumptions were used with regards to the modelled benefits of treatment with selumetinib and outcomes under current clinical management. **The overall approach was deemed appropriate, with the underlying clinical rationale and key model assumptions validated by UK clinical experts in NF1 PN** (Section 10.6.2 and 12.1).

Selumetinib represents a cost-effective use of NHS resources with an ICER of £93,169 per QALY versus current clinical management, which is below the £100,000 per QALY willingness-to-pay threshold for highly specialised technologies. Selumetinib is expected to provide an additional [redacted] QALYs versus current clinical management, which is consistent with the benefit of associated lifelong impact of preventing PN growth from childhood, where PN volume growth has been observed to be most rapid. These benefits are associated with an incremental cost of [redacted]. **The robustness of the cost-effectiveness results was demonstrated through extensive scenario and sensitivity analyses, which showed good consistency with the base case ICERs**.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Long-term data from the extended follow-up of patients treated with selumetinib, once available, may allow the replacement or refinement of current conservative assumptions covering the disease progression in adult patients, and allow for more robust modelling of the treatment benefit of selumetinib across a patient's entire lifetime.

Alternative approaches could be explored if larger datasets become available that could allow for a more conventional health state-based model (or other regression-based approaches) to be considered.

13 Cost to the NHS and Personal Social Services

Summary of Section D13

- The eligible population for selumetinib treatment is small and well-defined. The size of the population eligible for selumetinib treatment in England has been calculated at 37 patients. This is based on:
    - Detailed hospital episode statistics records for the primary diagnosis of neurofibromatosis (NF) for patients between 3 to 17 years old (inclusive). This is likely to slightly overestimate the number of patients with NF1, given the additional patients with NF2 and schwannomatosis.
    - The proportion of paediatric patients who have a PN (25%)
    - Of whom are identified to have symptomatic (55%), inoperable PN (50%)
- Over the next five years, an additional [redacted] to [redacted] patients per year are estimated to be eligible for treatment with selumetinib, accounting for the anticipated compliance and uptake rates of selumetinib. Once accounting for treatment discontinuation, there would be an estimated [redacted] patients in the first year rising to [redacted] patients in the fifth year
- The budget impact estimates include only the drug acquisition costs associated with selumetinib; unit costs and dosing requirements are consistent with those detailed for the cost-effectiveness analysis in Section 12.3. Treatment with selumetinib may reduce symptom management costs associated with the PNs. These costs were expected to be low, relative to the cost of selumetinib, and have conservatively been excluded from the analysis as the associated impact on the final budget impact is likely to be negligible
- Total cost to NHS England in the first year of selumetinib is estimated to be [redacted] in the first year, and [redacted] in the fifth year, which is far below the £20 million threshold required for the budget impact test

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

Table D37 presents the projected prevalent population of NF1 patients with symptomatic, inoperable PN that will be eligible for treatment with selumetinib in England.

The anticipated license for selumetinib is for treatment initiation to begin in paediatric patients aged 3–17 years. The ONS estimates that 10,140,338 children are in this age range in England and Wales (mid-2020).[77] The total number of admissions of

neurofibroma in England was 538, based on hospital episode statistics for primary diagnosis of neurofibromatosis (assumed mostly NF1).

Research suggests that approximately 25% of NF1 paediatric patients will have a PN.[6, 7] Approximately 55% of PN are symptomatic.[78] An inoperable PN is defined as being unable to be completely surgically resected without risk of substantial morbidity due to encasement of, or proximity to, vital structures, invasiveness, or level of vascularisation. It is estimated that between 43% and 57% of PN may fulfil this definition of inoperability; therefore, the midpoint of this range is used (50%).[15, 79] This leads to an estimated 37 prevalent paediatric NF1 patients with symptomatic PN eligible for selumetinib in England within the licensed population.

Table D37. Projected eligible population size in England

Population	Estimated proportion	Estimated number	Source
Total population aged 3–17 years in England	-	10,140,338	Office for National Statistics, mid-2020[77]
Total number of admissions of neurofibromatosis (aged 3-17)	-	538	Hospital Episode Statistics - Primary diagnosis: 4-character table, neurofibromatosis (non-malignant) Q85.0, 2019-2020; assumed mostly NF1[91]
Proportion of paediatric patients with NF1 who have PN	25%	135	Nguyen et al. 2011[6] and Boulanger et al. 2005[7] (mean average taken)
PN which are symptomatic	55%	74	Nguyen et al. 2012[78] (upper end of range taken for a conservative estimate)
Proportion of PN which are inoperable	50%	37	Waggoner et al. 2000[79] Serletis et al. 2007[15] (Mean average taken)
Total eligible patient population	**-**	**37**	Calculated from above

Abbreviations: MEKi: mitogen-activated protein kinase inhibitor; NF1: neurofibromatosis type 1; PN: plexiform neurofibroma.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

Using the eligible population estimated in Table D37, Table D38 presents the estimated uptake of selumetinib over the next five years. The uptake and compliance rates of selumetinib are based on internal AstraZeneca estimates. The analysis incorporates an average treatment discontinuation value per year, based on the SPRINT Phase II Stratum I TTD (Section 12.2).

Table D38. Estimated numbers of patients over the first five years

Estimated numbers	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients (paediatric symptomatic, inoperable NF1 PN)	37	37	37	37	37
Selumetinib uptake/compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients remaining on selumetinib treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

As previously described, in the absence of an active treatment available for NF1 PN, patients are already monitored by annual routine MRI scans and/or physical examinations. No additional tests or investigations would be required for identifying or selecting patients for treatment with selumetinib.

Patients receiving selumetinib are likely to require monitoring for the duration of treatment, which may include up to two additional MRI scans per year and there may be a small amount of costs associated with managing AEs (Sections 12.3.5 and 12.3.6). As these costs are minimal, they have not been incorporated into the budget impact model. The costs associated with BSC have also not been included within the analysis, as selumetinib will be delivered in addition to BSC. Whilst selumetinib may reduce the need for symptomatic care, the incremental impact is likely to be minimal.

13.4 Describe any estimates of resource savings associated with the use of the technology.

Relevant discussion is included in Sections 12.3.8, 12.3.9 and 14. Selumetinib is likely to reduce the need for medical facilities and technologies used to treat PN-associated morbidities, including a reduction in pain medication, in airway-related interventions such as tracheostomy and, as a result of improved HRQoL, reduced need for psychological support.[34, 86] The associated cost savings are expected to be low, relative to the cost of selumetinib, and have conservatively been excluded from the analysis, as the associated impact on the final budget impact is likely to be small.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Due to the general lack of data in the NF1 PN population, there are several opportunities for resource savings that are not quanitfiable for inclusion in this analysis.

Please see Sections 12.3.8, 12.3.9 and 14 for further discussion.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Selumetinib treatment may have a wider societal impact by alleviating the burden of disease on patients, parents and carers, resulting in a broad range of cost-savings.

Clinical experts noted that NF1 PN can negatively influence career prospects and job choices throughout life, due to the physical ad functioning impairments associated with PN. [28] Selumetinib can therefore open opportunities that may not otherwise have been possible. In terms of the wider societal benefits, this may result in productivity gains for patients, parents and carers more broadly. [28]

Please see Sections 12.3.8, 12.3.9 and 14 for further discussion.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The estimated budget impact of selumetinib over the next 5 years is shown in Table D39 below. Due to the very low numbers of patients anticipated to receive treatment with selumetinib, the results are far below £20 million in any of the first three years following the introduction of selumetinib; as such, it lies below the threshold of the NHS budget impact test.

Table D39. Estimated selumetinib budget impact

Results	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients (paediatric symptomatic, inoperable NF1 PN)	37	37	37	37	37
Population on treatment with selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive current clinical management (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without selumetinib*	£0	£0	£0	£0	£0
Cost of treatment pathway with selumetinib (net budget impact)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Totals may not appear to be the sum of the parts due to rounding.
* Simplified analysis assumes that there is no cost associated with BSC, as these are minimal. As selumetinib will be administered in addition to BSC, any incremental impact would be negligible.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The analysis is considered to provide an accurate estimate of the budget impact associated with selumetinib. Although it is noted that data are generally limited within the NF1 PN setting as it is a rare and heterogenous disease, these data are the best evidence-based estimates for the indicated population. Although there may be some variability in the exact inputs used to derive patient numbers, the impact of changing these would not substantially influence the budget impact results, which would continue to be below the £20 million threshold for the budget impact test.

Section E – Impact of the technology beyond direct health benefits

Summary of Section E14

- Selumetinib is anticipated to have substantial benefits associated with HRQoL improvements for patients and parents/carers as a result of reductions in PN volumes and improvements in PN-associated morbidities including pain and motor morbidities[34]
- In addition to improvements in parent/carer HRQoL, selumetinib is expected to lead to a reduction in parent/carer productivity loss, presenteeism and absenteeism, as a result of a reduction in the amount of caregiving required by their child
- Treatment of NF1 PN patients with selumetinib may lead to cost savings to local councils and government bodies as a result of a reduction in days of school missed by patients, and reduced child and adult disability support claims, as a result of durable reductions in PN volumes and the number and severity of PN-associated morbidities
- Selumetinib represents a step-change in the treatment of patients with NF1 PN; use of selumetinib will enable the investigation of the long-term benefits of disease-modifying therapy for NF1 PN patients, which may lead to further innovations in care
- Selumetinib will be delivered from the two UK NF1 PN specialist centres by experts in the treatment of patients with NF1 PN, allowing safe and effective use of the technology

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

A substantial proportion of the anticipated benefits of selumetinib are associated with improvements in HRQoL for patients and parents/carers (see Section 9.6.1):

- Results from Stratum I of the SPRINT Phase II trial demonstrate that selumetinib treatment leads to significant and durable reductions in PN volume, accompanied by improvements in PN-associated morbidities and patient HRQoL[18, 34]

- Reductions in morbidities including disability, pain and pain interference with daily functioning would be expected to improve the ability of patients to perform normal daily activities of living[34]

- The reductions in disfigurement possible with selumetinib treatment are expected to reduce the social stigma experienced by patients, and improve patient emotional wellbeing (including reductions in anxiety)[18, 19, 25, 26, 34]

- Parents/carers are also likely to experience improved HRQoL, due to reduced anxiety over the course of the patient's disease, and improvements in their child's emotional and social wellbeing[18, 19, 25, 26, 34]

Further details of the anticipated impact of selumetinib on patient and parent/carer HRQoL are provided in Section 9.6. In addition to improved HRQoL, parents/carers are likely to benefit from improved productivity and a reduction in out-of-pocket expenses as a result of reduction in the need to provide care and support for their child (see Section 14.3 for further details).[29]

14.2 List the costs (or cost savings) to government bodies other than the NHS.

While the impact of selumetinib on cost and cost savings to UK government bodies has not been explicitly investigated, selumetinib may be expected to bring cost savings to government bodies other than the NHS as a result of: improvements in patients' daily lives, reduced patient disability, and improved parent/carer productivity.

Children with NF1 PN are likely to miss days of school;[25] in part due to the need for medical treatment and hospitalisation as a result of PN-associated morbidities, and also as a direct result of morbidity. Common morbidities include trunk/limb PNs that impair a child's ability to sit still in class.[28] This results in time being diminished school attendance, preventing patients from participating in lessons and building relationships with their peers. UK clinicians have highlighted that education and employment prospects are especially impacted in patients with NF1 PN.[28]

As a result of selumetinib treatment, children with NF1 PN would have a reduced number and/or severity of PN-associated morbidities (see Section 9.6.1). This would mean children with NF1 PN treated with selumetinib are likely to require less support with their learning in order to catch up on the school time they have missed, in turn leading to cost savings for local councils.

An additional benefit of the reduction in severity and number of PN-associated morbidities, especially those relating to physical functioning, may be a reduction in Disability Living Allowance (DLA) claims for children with NF1 PN. These cost savings would result from the reduction in PN-associated disability associated with selumetinib

treatment; patients treated with selumetinib have shown improvements in motor function including strength and range of movements and reductions in pain interference with daily living.[18] As treated paediatric patients become adults, they are likely to be more independent (than untreated patients), requiring less disability (or other welfare) payments.[28] Selumetinib treatment would also be expected to mean that patients are more likely to be employed, thereby requiring less unemployment benefits.[28]

Finally, cost savings may be made as a result of a reduced caregiving burden. The impact of PN-associated morbidities can place a significant financial burden on the parents, families and carers of patients with NF1 PN (see Section 7.2 Family and carer QoL). This financial burden can result from productivity loss and days missed from work,[29] as well as from out-of-pocket expenses associated with supporting patients (see Section 14.3). As selumetinib has demonstrated a positive impact on PN-associated morbidities, including disability-causing morbidities (see Section 9.6.1 Secondary outcomes: clinical outcome measures) the requirement for caregiving is anticipated to decrease. This would lead to a reduced impact on carer productivity.[28]

14.3 List the costs borne by patients that are not reimbursed by the NHS.

As the population eligible for selumetinib treatment are paediatric NF1 PN patients[61] the costs which are not reimbursed by the NHS are borne by their parents and carers.

Parents/carers are likely to experience a loss of income as a result of productivity loss due to their caring responsibilities (see Section 7.2 Family and carer QoL). As a result of caring for a child with NF1 PN, carers are affected by both absenteeism and presenteeism;[28] a survey of carers of NF1 PN identified that carers had missed an average of 6.9% of their working hours and had an average reduction of 17.3% of on-the-job effectiveness in the week preceding the survey.[29] This may have a corresponding impact on their career prospects and progression. In addition, some parents/carers may be required to invest in home adaptations and aids for children with PN-associated mobility difficulties, such as specialist wheelchairs and other mobility aids, wheelchair accessible cars, and ramps for the home.

Additional costs may arise as the patient enters adulthood and is no longer eligible for NHS paediatric function or support; this could include the costs associated with vision aids such as glasses for patients with PN-associated vision morbidities, and costs of prescriptions, such as for pain medication. Patients require a large amount of occupational health support.[28]

Selumetinib treatment has demonstrated improvements in PN-associated morbidities and patient HRQoL (see Section 9.6.1 Secondary outcomes: clinical outcome measures). As such, while not captured within the perspective of the cost-effectiveness model, selumetinib is anticipated to result in cost savings for patients and their families as a result of increased carer productivity and ability to work and a reduction in the need for home supports and supportive care for patients.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

UK clinicians were interviewed on aspects of care for patients with NF1 PN.[28] They reported that family members (typically parents) will be the primary caregiver for patients. While a formal quantification was not possible, it was noted that a substantial amount of time is devoted to care of patients by family members. This ranges from time taken out of work to accompany patients to check-ups and clinician visits, to extra time spent with patients during normal daily activities (often made more difficult by learning difficulties as a result of underlying NF1). Quite often, this caregiver impact will continue into adulthood where patients with NF1 PN are unable to find employment.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The Phase II Stratum I of the SPRINT clinical trial has investigated the efficacy and safety of selumetinib in paediatric patients with symptomatic, inoperable NF1 PN. SPRINT Phase II Stratum I enrolled 50 patients and examined the effect of selumetinib treatment on PN growth and volume, PN-associated morbidities and patient HRQoL.[18] This study demonstrated that selumetinib is well tolerated and effective in reducing PN volume, increasing PFS and improving HRQoL in this patient population. Patients treated with selumetinib experienced improvements across a range of functional outcomes, representing a reduction in PN-associated morbidities.[18, 34, 42] Full details of SPRINT Phase II Stratum I study design and results can be found in Sections 9.4 and 9.6.

There are a number of ongoing studies investigating selumetinib in other patient populations:

- SPRINT Phase II Stratum II is investigating the use of selumetinib in paediatric patients with inoperable PN which have the potential to become symptomatic. Stratum II includes 25 patients and will provide evidence for selumetinib's potential to prevent PN-associated morbidities from developing, and therefore deficits in patient HRQoL, through reducing or halting PN growth and reducing PN volumes (see Section 4.1 for further details)[38]

- NCT02407405 is a Phase II study of selumetinib in adult patients aged ≥18 years old with symptomatic or progressive inoperable PN. This study is evaluating the response of PN to selumetinib in adult patients and its effects on pain, HRQoL and physical functioning for these patients; the study has so far enrolled 60 participants. NCT02407405 will provide evidence for the impact of selumetinib treatment during adulthood on PN-associated morbidities, and PN which remain progressive[119]

- NCT03649165 is a Phase I, open-label, single-centre, randomized crossover pharmacokinetics study of selumetinib, designed to investigate a granule formulation versus capsule formulation in both fasted and fed (low-fat) states. Development of the granule formulation aims to support dose flexibility and the use for patients unable to swallow capsules[173]

In addition to the studies investigating selumetinib in patients with NF1 PN, a HRQoL study has been performed in this population (see Section 10.4). This HRQoL study is instrumental in providing QoL information for both paediatric NF1 PN patients and their parents/carers, filling crucial evidence gaps for these populations, and providing vital data for the HRQoL life of NF1 PN patients in the absence of a disease-modifying treatment.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Selumetinib represents a step change in the management of NF1 PN. As the first licensed disease-modifying treatment for NF1 PN, selumetinib will provide an opportunity to understand the long-term impact of disease-modifying treatment for PN, opening the door for further innovations in the care of patients with symptomatic, inoperable PN.

Genetic testing is recommended as part of most recent, international diagnostic criteria for NF1 (please see Section 8 for further details).[101] The introduction of selumetinib is anticipated to act as catalyst for increased genetic testing for NF1 in the UK, particularly in light of the NHS Long Term Plan to expand routine genetic testing.[174] This will facilitate the identification and appropriate treatment of UK patients.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

Selumetinib is currently being offered to UK patients as part of the selumetinib EAP, with [redacted] patients in England currently receiving selumetinib through this scheme.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

The efficacy of selumetinib will continue to be reviewed through subsequent data cuts of the SPRINT trial.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

As described in Section 8, selumetinib will be delivered from the two UK NF1 PN specialist centres by clinicians experienced in the treatment and management of patients with NF1 PN;[28] indeed the MDT already has a MEK inhibitor clinic in operation.

Prescribing clinicians have the level of expertise required in the indicated population to ensure safe and effective use of the technology.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure beyond that already in place within the NHS will be required for the effective use of and equitable access to selumetinib for all eligible patients.[28]

Section F – Managed Access Arrangements

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

As outlined in Section 12.8.3, the results presented in this submission represent the first cost-effectiveness analysis including patients with NF1 PN. By necessity of the limited clinical data available, the analysis used a simple methodological approach and is likely to be conservative with regards to the modelled benefits of treatment with selumetinib, in particular with regards to outcomes in adult patients which make up the majority of the modelled time horizon. It was not possible to directly model clinical outcomes based on the primary outcome of SPRINT Phase II Stratum I (i.e. ORR) or the secondary outcome of target PN volume, in order to predict the utility values of patients, due to the heterogenous study patient population.

Ultimately, a simple yet conservative approach was taken to modelling, with treatment benefits captured in the form of PFS, a key secondary outcome of SPRINT Phase II Stratum I, and the corresponding benefit of selumetinib on patients' HRQoL associated with remaining progression-free.

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*
- *What evidence will be collected to reduce uncertainty*
- *How this evidence will be collected and analysed*
- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*
- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*
- *Funding arrangement, including any commercial proposals or financial risk management plans*
- *The roles and responsibilities of clinical and patient groups during the MAA*
- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

Using a single clinical endpoint to assess treatment outcomes in NF1 PN is challenging, owing to the heterogeneity in the location and severity of PNs; a variety of outcome measures are likely to be required.

Further data collection from patients on selumetinib treatment may help validate assumptions made in the economic model. Collection of progression data and tumour volume size while patients are on/off treatment would help validate assumptions in the model. Collection of tumour volume size in adult patients who have stopped selumetinib may be confirmatory of existing data suggesting that tumour growth effectively plateaus in adulthood (compared with substantial growth in younger childhood). Furthermore, linking this to collected patient pain and HRQoL data would help clarify the link between treatment and improved HRQoL outcomes.[108] However, the amount of data collection required, given the heterogeneity of the disease coupled with the size of the patient population, would likely prove prohibitive.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

Linking tumour size reduction and pain outcomes to improvements in HRQoL of UK patients is anticipated to be confirmatory of the approach to modelling undertaken to demonstrate the value of selumetinib in patients with NF1 PN.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Electronic Databases

The following electronic databases were searched:

- Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (searched via the Ovid SP platform, from 1946 to January 25, 2021)
- Embase (searched via the Ovid SP platform, from 1974 to 25 January 2021)
- The CDSR and CENTRAL, searched simultaneously via The Cochrane Library Wiley online platform, Issue 1 of 12, January 2021
- The DARE, searched via the University of York CRD platform, Issue 2 of 4, April 2015

Full search strategies used in the database searches can be found in Section 17.1.4.

Conference Searches

A manual search of the following conference proceedings from the last three years (2018–2020) was performed:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
    - ISPOR 2018 (May 2018, Baltimore)
    - ISPOR Europe 2018 (November 2018, Barcelona)
    - ISPOR 2019 (May 2019, New Orleans)
    - ISPOR Europe 2019 (November 2019, Copenhagen)

    - ISPOR 2020 (May 2020, Virtual)
    - ISPOR Europe 2020 (November 2020, Virtual)
- Children's Tumor Foundation NF Conference
    - NF Conference 2019 (September 2019, San Francisco)
    - NF Conference 2020 (June 2020, Philadelphia)
- Joint Global Neurofibromatosis Conference (JGNC) 2018 (November 2018, Paris; this event combined the Children's Tumor Foundation NF Conference and European Neurofibromatosis Meeting in that year)
- European Society for Medical Oncology (ESMO) Congress
    - ESMO 2018 (October 2018, Munich)
    - ESMO 2019 (September–October 2019, Barcelona)
    - ESMO 2020 (September 2020, Virtual)
- American Society of Clinical Oncology (ASCO) Annual Meeting
    - ASCO 2018 (June 2018, Chicago)
    - ASCO 2019 (May–June 2019, Chicago)
    - ASCO 2020 (May–June 2020, Virtual)
- International Symposium on Pediatric Neuro-Oncology (ISPNO)
    - ISPNO 2018 (June–July 2018, Denver)
    - ISPNO 2020 (December 2020, Karuizawa)
- American Society of Pediatric Hematology/Oncology (ASPHO)
    - ASPHO 2018 (May 2018, Pittsburgh)
    - ASPHO 2019 (May 2019, New Orleans)
    - ASPHO 2020 (May 2020, Virtual)

Conference searches were limited to the past three years on the basis that any high-quality data published at conferences before this point, are likely to have been published in a journal article, so detected in the electronic database searches.

Search strategies used in the conferences can be found in Section 17.1.5.

Bibliography Searches

The bibliographies of any relevant SLRs and (N)MAs were manually searched to identify any additional, relevant studies for inclusion.

Supplementary Searches

In addition to the database and grey literature searching performed, a manual search of materials provided by AstraZeneca was conducted. These materials included:

- A TLR conducted in 2019 on NF1 PN clinical studies
- A TLR conducted in 2020 to capture HRQoL instruments in NF1

Clinical Trial Registries

In order to identify any unpublished clinical trials, an additional search using ClinicalTrials.gov was undertaken to identify any unpublished studies in the NF1 or PN disease areas. Relevant studies were cross-checked against the results obtained from the searches for published clinical evidence to ensure no duplication or incorrect classification of studies. The search strategy used can be found in 17.1.5.

17.1.2 The date on which the search was conducted.

Searches were conducted over the time-period presented in Table 1 between January and February 2021.

Table 1. Dates on which searches were conducted

Resource searched	Date conducted
Electronic databases (MEDLINE, Embase, CDSR, CENTRAL, DARE)	26th January 2021
Conference proceedings (ASPHO, ASCO, Children's Tumor Foundation NF Conference, ESMO, ISPNO, ISPOR, JGNC)	5th February 2021
Manual bibliography searches of relevant SLRs/(N)MAs	5th February 2021
Supplementary searches of AstraZeneca material	22nd January 2021
Clinical Trial Registries (ClinicalTrials.gov)	28th January 2021

Abbreviations: ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; ESMO: European Society for Medical Oncology; ISPNO: International Symposium on Pediatric Neuro-Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; JGNC: Joint Global Neurofibromatosis Conference; (N)MA: (network) meta-analyses; SLR: systematic literature review.

17.1.3 The date span of the search.

No date limit was applied to the electronic database, ClinicalTrials.gov, bibliography, or validation searches. All conference abstracts reviewed were limited to those published in the past three years (2018−2020).

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search terms used in MEDLINE and Embase are presented in Table 2 and Table 3 respectively. Search terms for CDSR and CENTRAL are presented in Table 4. Search terms for DARE are presented in Table 5.

Table 2. Search terms used in MEDLINE (searched via Ovid SP on 26th January 2021)

	#	Searches	Results
Disease area: NF1 PN	1	exp Neurofibromatosis 1/	9,853
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kf.	7,977
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kf.	8,325
	4	or/1-3	16,491
	5	neurofibroma/ or Neurofibroma, Plexiform/	4,393
	6	(plexiform neurofibroma$ or plexiform neuroma$).ti,ab,kf.	1,301
	7	or/5-6	5,038
Study design: RCTs	8	4 and 7	1,667
	9	randomized controlled trials as topic/	139,849
	10	randomized controlled trial/	521,383
	11	random allocation/	104,479
	12	double blind method/	161,985
	13	single blind method/	29,608
	14	clinical trial/	527,065
	15	controlled clinical trial/	94,038
	16	multicenter study/	286,869
	17	clinical trial, phase i.pt.	21,176
	18	clinical trial, phase ii.pt.	34,064
	19	clinical trial, phase iii.pt.	17,787
	20	clinical trial, phase iv.pt.	2,029
	21	controlled clinical trial.pt.	94,038
	22	randomized controlled trial.pt.	521,383

	23	multicenter study.pt.	286,869
	24	clinical trial.pt.	527,065
	25	exp clinical trials as topic/	351,447
	26	(clinical adj trial$).ti,ab,kf.	399,209
	27	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	178,171
	28	placebos/	35,309
	29	placebo$.ti,ab,kf.	223,422
	30	(allocat$ adj2 random$).ti,ab,kf.	36,918
	31	(Randomi?ed adj2 trial$).ti,ab,kf.	343,839
	32	rct.ti,ab,kf.	25,331
	33	or/9-32	1,788,474
Study design: Non-RCTs/observational studies	34	exp Epidemiologic studies/	2,600,736
	35	exp case control studies/	1,136,817
	36	exp Cohort Studies/	2,081,389
	37	Case control.ti,ab,kf.	132,372
	38	(cohort adj (study or studies)).ti,ab,kf.	230,597
	39	cohort analy$.ti,ab,kf.	9,555
	40	(follow up adj (study or studies)).ti,ab,kf.	52,207
	41	(observational adj (study or studies)).ti,ab,kf.	118,338
	42	Longitudinal$.ti,ab,kf.	281,317
	43	retrospective$.ti,ab,kf.	797,365
	44	Cross sectional.ti,ab,kf.	383,591
	45	Cross-sectional studies/	351,013
	46	exp Longitudinal Studies/	141,470
	47	exp Follow-Up Studies/	654,895
	48	exp Prospective Studies/	561,249
	49	exp Retrospective Studies/	866,397
	50	(Follow up adj (study or studies)).ti,ab,kf.	52,207
	51	(Prospective adj (study or studies)).ti,ab,kf.	182,190
	52	(evaluation adj (study or studies)).ti,ab,kf.	6,131
	53	(epidemiologic adj (study or studies)).ti,ab,kf.	27,249
	54	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kf.	6,094
	55	(Open-label adj (trial$ or stud$)).ti,ab,kf.	11,776
	56	Non-blinded stud$.ti,ab,kf.	133
	57	(chart adj3 review).ti,ab,kf.	42,206
	58	or/34-57	3,347,297
Exclusion Terms	59	exp animals/ not exp humans/	4,780,075
	60	(comment or editorial).pt.	1,273,548

	61	historical article/	361,854
	62	or/59-61	6,344,185
Combined	63	8 and (33 or 58)	309
	64	63 not 62	**308**

Database(s): Searches included Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, from 1946 to January 25, 2021

Table 3. Search terms used in Embase (searched via Ovid SP on 26th January 2021)

	#	Searches	Results
Disease area: NF1 PN	1	exp neurofibromatosis type 1/	3,605
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kw.	10,295
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kw.	12,188
	4	or/1-3	17,002
	5	neurofibroma/	6,342
	6	(plexiform neurofibroma$ or plexiform neuroma$).ti,ab,kw.	1,605
	7	or/5-6	7,001
	8	4 and 7	2,333
Study design: RCTs	9	"randomized controlled trial (topic)"/	194,891
	10	randomized controlled trial/	641,842
	11	clinical trial/	998,361
	12	exp "clinical trial (topic)"/	344,523
	13	controlled clinical trial/	466,048
	14	multicenter study/	276,039
	15	randomization/	89,812
	16	single blind procedure/	41,600
	17	double blind procedure/	180,633
	18	crossover procedure/	65,906
	19	placebo/	361,846
	20	phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	170,780
	21	(clinical adj trial$).ti,ab,kw.	574,705
	22	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kw.	247,642
	23	placebo$.ti,ab,kw.	321,323
	24	(allocat$ adj2 random$).ti,ab,kw.	45,713
	25	(Randomi?ed adj2 trial$).ti,ab,kw.	463,855
	26	rct.ti,ab,kw.	42,617
	27	or/9-26	2,484,002
Study design: Non-RCTs/observational studies	28	exp epidemiology/	3,604,639
	29	exp case control study/	185,272
	30	exp cohort analysis/	662,004

	31	Case control.ti,ab,kw.	173,389
	32	(cohort adj (study or studies)).ti,ab,kw.	334,387
	33	cohort analy$.ti,ab,kw.	14,180
	34	(Follow up adj (study or studies)).ti,ab,kw.	68,688
	35	(observational adj (study or studies)).ti,ab,kw.	183,647
	36	Longitudinal$.ti,ab,kw.	379,488
	37	retrospective$.ti,ab,kw.	1,318,938
	38	Cross sectional.ti,ab,kw.	502,416
	39	Cross-sectional study/	390,149
	40	exp Longitudinal study/	150,464
	41	exp follow up/	1,637,236
	42	exp retrospective study/	1,021,601
	43	exp observational study/	220,005
	44	(Prospective adj (study or studies)).ti,ab,kw.	274,022
	45	(evaluation adj (study or studies)).ti,ab,kw.	8,667
	46	(epidemiologic adj (study or studies)).ti,ab,kw.	34,755
	47	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kw.	12,631
	48	(Open-label adj (trial$ or stud$)).ti,ab,kw.	20,398
	49	Non-blinded stud$.ti,ab,kw.	193
	50	(chart adj3 review).ti,ab,kw.	87,083
	51	or/28-50	6,646,318
Exclusion terms	52	("conference abstract" or "conference review").pt.	4,005,664
	53	limit 52 to yr="1974-2018"	3,038,161
	54	exp animals/ not exp humans/	4,750,859
	55	(comment or editorial).pt.	682,497
	56	historical article/	1
	57	or/52-56	8,180,843
Combined	58	8 and (27 or 51)	772
	59	58 not 57	**660**

Database: Embase from 1974 to January 25, 2021

Table 4. Search terms used in CDSR and CENTRAL (searched simultaneously via the Cochrane Library Wiley online platform on 26th January 2021)

#	Searches	Results
1	[mh “neurofibromatosis 1”]	54
2	("1" or i or peripheral or von Recklinghausen) near/2 neurofibroma*:ti,ab,kw	120
3	(NF1 or NFI or NF-1 or NF-I):ti,ab,kw	232

4	{or #1-#3}	261
5	[mh ^“neurofibroma”] OR [mh ^“neurofibroma, Plexiform”]	43
6	(plexiform neurofibroma* or plexiform neuroma*):ti,ab,kw	16
7	{or #5-#6}	54
8	#4 and #7	42
9	#8 in Trials	**42**
10	#8 in Cochrane Reviews, Cochrane Protocols	**0**

Database: For both CDSR and CENTRAL, the most recent issue searched was Issue 1 of 12, January 2021.

Table 5. Search terms for DARE (searched via the University of York CRD platform on 26th January 2021)

#	Searches	Results
1	MeSH DESCRIPTOR Neurofibromatosis 1 EXPLODE ALL TREES	2
2	((neurofibroma* adj1 ("1" or i or peripheral or von Recklinghausen)))	6
3	((NF1 or NFI or NF-1 or NF-I))	5
4	MeSH DESCRIPTOR Neurofibroma	3
5	MeSH DESCRIPTOR Neurofibroma, Plexiform	0
6	((plexiform neurofibroma* or plexiform neuroma*))	1
7	(#1 OR #2 OR #3 OR #4)	7
8	(#5 OR #6)	1
9	(#7 and #8)	1
10	(#9) IN DARE	**0**

Database: DARE, the most recent issue searched was Issue 2 of 4, April 2015

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Conference searches

Abstract books (where available) or the relevant conference website were searched for eight selected conferences for the past three years, in order to identify any additional studies eligible for inclusion in the SLR. The total results and number of included records for each conference are presented in Table 6.

Table 6. Search strategies for congress searching (performed between 21st January 2021 and 5th February 2021)

Conference	Link	Search Strategy	Number screened; included
ASCO Annual Meeting: 2018	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: **Meeting:** ASCO Annual Meeting **Date:** 2018 The following string was then searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:"von Recklinghausen")	40 screened; 0 included
ASCO Annual Meeting: 2019	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: **Meeting:** ASCO Annual Meeting **Date:** 2019 The following string was then searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:"von Recklinghausen")	57 screened; 0 included
ASCO Annual Meeting: 2020	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: **Meeting:** ASCO Virtual Scientific Program **Date:** 2020 The following string was then searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:"von Recklinghausen")	47 screened; 0 included
ASPHO 2018	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CO	The 2018 conference website was searched in turn for the following terms: • Neurofibrom*	2 screened; 0 included

	NF=AM18&ssoOverride=OFF&USERPID=PUBLIC	• "NF-1" • NF1 • Plexiform • Von Recklinghausen's	
ASPHO 2019	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM19&ssoOverride=OFF&USERPID=PUBLIC	The 2019 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	3 screened; 0 included
ASPHO 2020	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM20&ssoOverride=OFF&USERPID=PUBLIC	The 2020 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	4 screened; 1 included
Children's Tumor Foundation NF Conference: 2019[a]	https://www.ctf.org/get-involved/nf-conference	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	145 screened; 3 included
Children's Tumor Foundation NF Conference: 2020[a]	https://www.ctf.org/get-involved/nf-conference	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1	59 screened; 3 included

		• Von Recklinghausen's	
ESMO Congress 2018	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress	The 2018 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	6 screened; 0 included
ESMO Congress 2019	https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress	The 2019 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	14 screened; 0 included
ESMO Congress 2020	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020	The 2020 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	5 screened; 0 included
ISPNO: 2018[b]	http://ispno2018.com/	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	377 screened; 0 included

ISPNO: 2020[b]	http://ispno2020.umin.jp/	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	49 screened; 0 included
ISPOR Annual European Meeting 2018	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2018-11, ISPOR Europe 2018, Barcelona, Spain" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual European Meeting 2019	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2019-11, ISPOR Europe 2019, Copenhagen, Denmark" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual European Meeting 2020	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2020-11, ISPOR Europe 2020, Milan, Italy" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom*	5 screened; 0 included

		• Von Recklinghausen's	
ISPOR Annual International Meeting 2018	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2018-05, ISPOR 2018, Baltimore, MD, USA" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual International Meeting 2019	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2019-05, ISPOR 2019, New Orleans, LA, USA" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual International Meeting 2020	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2020-05, ISPOR 2020, Orlando, FL, USA" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
JGNC 2018[a]	http://www.nf-paris2018.com/EventPortal/Information/NF2018/WELCOME.aspx	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1	291 screened; 5 included

		• Von Recklinghausen's	

Footnotes: [a]In 2018, the Children's Tumor Foundation NF Conference was combined with the European Neurofibromatosis Meeting and ran as JGNC 2018; [b]biennial conference

Abbreviations: ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; ESMO: European Society for Medical Oncology; FL: Florida; ISPNO: International Symposium on Pediatric Neuro-Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; JGNC: Joint Global Neurofibromatosis Conference; LA: Louisiana; MD: Maryland; NF1: type 1 neurofibromatosis; USA: United States of America.

ClinicalTrials.gov

The terms in Table 7 were searched sequentially using the "condition or disease" search function.

Table 7. Search terms used for ClinicalTrials.gov (searched on 28th January 2021)

#	Condition	Other parameters	Results
1	Neurofibromatosis Type 1 or Plexiform Neurofibroma	Other terms: none Study type: any First posted: any time Study results: all Recruitment status: all	206 screened; 2 included

17.1.6 The inclusion and exclusion criteria.

Eligibility criteria for the inclusion and exclusion of studies are presented in Table C1 in Section 9.1.1.

17.1.7 The data abstraction strategy.

The most stringent record screening process as recommended by the Cochrane Collaboration was followed.[175] The title and abstract of each record were reviewed against the eligibility criteria by two independent reviewers. Where the applicability of the inclusion criteria was unclear, articles were included at this stage to ensure that all potentially relevant studies were captured. The two independent reviewers then compared their results, and any disagreements were resolved by discussion until a consensus was met, with a third independent reviewer asked to arbitrate when necessary.

For studies meeting the eligibility criteria after title and abstract review, the full text was reviewed against the eligibility criteria by two independent reviewers. Articles with insufficient information to ensure it meet the eligibility criteria were excluded at this stage, to ensure that only relevant articles were ultimately included in the SLR. Again, two independent reviewers compared results, and any conflicts were resolved by discussion or the arbitration of a third independent reviewer.

Key information from studies meeting the eligibility criteria after full-text review were extracted by a single reviewer into a pre-specified data extraction grid in Microsoft Word. Any data extracted were verified for accuracy by a second, independent reviewer.

17.1.8 Included and excluded study tables.

Table 8. List of studies included in the clinical SLR

#	Study name	Citation
Published studies		
1	Baldo 2020	Baldo F, Grasso AG, Cortellazzo Wiel L, et al. Selumetinib in the Treatment of Symptomatic Intractable Plexiform Neurofibromas in Neurofibromatosis Type 1: A Prospective Case Series with Emphasis on Side Effects. Pediatric Drugs 2020;22:417-423.

#	Study name	Citation
2	Espirito Santo 2020	Espirito Santo V, Passos J, Nzwalo H, et al. Selumetinib for plexiform neurofibromas in neurofibromatosis type 1: a single-institution experience. Journal of Neuro-Oncology 2020;147:459-463.
3	Kudek 2019	Kudek M, Knipstein, J., Zimbric, K. and Schloemer, N. Mek-ing a plan to treat NF: Safe delivery of mek inhibitors for inoperable plexiform neurofibromas. Pediatric Blood & Cancer 2019;66:S105-S106.
4	NCT02407405	CT.gov. MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas, 2020.
5		Martin S. Patient Reported Outcomes (PROs) Document Clinical Benefit among Adults with NF1 and Inoperable Plexiform Neurofibromas (PNs) on a Phase II Trial of the MEK 1/2 Inhibitor Selumetinib. Children's Tumor Foundation NF Conference 2019, 2019.
6		O'Sullivan Coyne GH, Gross AM, Dombi E, et al. Phase II trial of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886 Hydrogen Sulfate) in adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Journal of Clinical Oncology 2020;38:3612-3612.
7		O'Sullivan Coyne G. Phase II Trial of the MEK 1/2 Inhibitor Selumetinib (AZD6244, ARRY-142886 Hydrogen Sulfate) in Adults with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN). Children's Tumor Foundation NF Conference 2019, 2019.
8		O'Sullivan Coyne G. Phase II Trial of the MEK 1/2 Inhibitor Selumetinib (AZD6244, ARRY-142886 Hydrogen Sulfate) in Adults with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN). Children's Tumor Foundation NF Conference 2020, 2020.
9		Jackson S, Baker E, Gross A, et al. RARE-07. The Effect of Selumetinib On Spinal Neurofibromas In Patients With Nf1. Neuro-Oncology 2018;20:vi237-vi237.[a]
10		Jackson S, Baker EH, Gross AM, et al. The MEK inhibitor selumetinib reduces spinal neurofibroma burden in patients with NF1 and plexiform neurofibromas. Neuro-oncology Advances 2020;2:vdaa095.[a]
11		Jackson S. Burden and Feasibility of Functional Evaluations and Patient Reported Outcome (PRO) Measures in SPRINT: A Phase II Trial of the MEK Inhibitor Selumetinib (AZD6244, ARRY-142886) for Children with Neurofibromatosis Type 1 (NF1). Joint Global Neurofibromatosis Conference 2018, 2018.[a]
12	Passos 2020	Passos J, Nzwalo H, Azevedo M, et al. Dramatic Improvement of a Massive Plexiform Neurofibroma After Administration of Selumetinib. Pediatric Neurology 2020;105:69-70.
13	SPRINT: Phase I	Dombi E, Baldwin A, Marcus LJ, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. New England Journal of Medicine 2016;375:2550-2560.
14		CT.gov. AZD6244 Hydrogen Sulfate for Children With Nervous System Tumors, 2021.[b]
15		Dombi E. Factors Contributing to the Response of Children with NF1 and Plexiform Neurofibromas to Selumetinib. Children's Tumour Foundation NF Conference 2020, 2020.[c]

#	Study name	Citation
16	SPRINT: Phase II, Stratum 1	Gross A. Assessment of Pulmonary Function in Patients with Neurofibromatosis Type 1 and Airway Associated Plexiform Neurofibromas Before and After Treatment with Selumetinib. Children's Tumor Foundation NF Conference 2019, 2019.
17		Gross A. SPRINT: Phase II Study of the MEK 1/2 Inhibitor Selumetinib (AZD6244, ARRY-142886) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN). Joint Global Neurofibromatosis Conference 2018, 2018.
18		Gross AM, Wolters P, Baldwin A, et al. SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Journal of Clinical Oncology 2018;36:10503-10503.
19		Gross A, Wolters, P., Baldwin, A et al. Sprint: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Neuro-Oncology 2018;20:i143-i144.
20		Gross AM, Wolters PL, Dombi E, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. New England Journal of Medicine 2020;382:1430-1442.
21		Hampton C. Lack of Retinal Toxicity in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN) Treated on SPRINT: A Phase II Trial with the MEK Inhibitor Selumetinib. Joint Global Neurofibromatosis Conference 2018, 2018.
22		Wolters P. Prospective Patient-Reported Outcomes (PROs) Document Clinical Benefit in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PNs) on SPRINT: a Phase II Trial of the MEK 1/2 Inhibitor Selumetinib. Joint Global Neurofibromatosis Conference 2018, 2018.
23		Pichard D. Cutaneous Adverse Events in SPRINT: A Phase 2 Trial of the MEK Inhibitor Selumetinib for Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN). Joint Global Neurofibromatosis Conference 2018, 2018.[d]
24	SPRINT: Phase II, Stratum 2	Glassberg B GA, Dombi E, Baldwin A, et al. Selumetinib In Children with Clinically Asymptomatic Inoperable Nf1 Related Plexiform Neurofibromas. American Society of Pediatric Hematology/Oncology (ASPHO) Conference 2020, 2020.
25		Glassberg B. Selumetinib in Children with Clinically Asymptomatic Inoperable Neurofibromatosis Type 1 Related Plexiform Neurofibromas. Children's Tumor Foundation NF Conference 2020, 2020.

Footnotes: [a]Studies are pooled analyses reporting data on both SPRINT Phase II, stratum 1 and NCT02407405, [b]Study is the ClinicalTrials.gov record associated with SPRINT (Phase I, Phase II Stratum 1, and Phase II Stratum 2), [c]Study is a pooled analysis reporting data on SPRINT trials (Phase I, Phase II Stratum 1, and Phase II Stratum 2), [d]Study is a pooled analysis reporting data on SPRINT Phase II trials (Phase II Stratum 1, and Phase II Stratum 2)

Table 9. List of studies excluded in the clinical SLR at full-text review stage, and reasoning for exclusion

#	Citation	Reason for exclusion
1	Babovic-Vuksanovic D, Ballman K, Michels V, et al. Phase II trial of pirfenidone in adults with neurofibromatosis type 1. Neurology 2006;67:1860-2.	No relevant outcomes reported
2	Bano S, Prasad A, Yadav SN, et al. Elephantiasis neuromatosa of the lower limb in a patient with neurofibromatosis type-1: A case report with imaging findings. Journal of Pediatric Neurosciences 2010;5:59-63.	Irrelevant intervention
3	Bavle A, Choudhry F, Gavula T, et al. NFM-08. Safety And Efficacy Of Trametinib In The Management Of Children With Rasopathies. Neuro-Oncology 2018;20:i144-i144.	Irrelevant population
4	Bergqvist C, Servy A, Valeyrie-Allanore L, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet Journal of Rare Diseases 2020;15 (1) (no pagination).	Irrelevant study design
5	Calderon Miranda W.G CC, Salvador Hernandez H, Barber I,. MRI Volumetric assessment neurofibromas for the evaluation of the efficacy of MEK inhibitors treatment. Pediatric Radiology 2019;49:S308.	No relevant outcomes reported
6	Citak EC, Oguz A, Karadeniz C, et al. Management of plexiform neurofibroma with interferon alpha. Pediatric Hematology and Oncology 2008;25:673-678.	Irrelevant intervention
7	Copley-Merriman C, Yang X, Juniper M, et al. PRO85 Impact Of Neurofibromatosis Type 1 And Plexiform Neurofibromas On Patient-Reported Health-Related Quality Of Life. Value in Health 2020;23:S344.	Irrelevant study design
8	Darcy C, Ullrich NJ. A 15-Month-Old Girl Presenting With Clitoromegaly and a Chest Mass. Seminars in Pediatric Neurology 2018;26:128-131.	Irrelevant population
9	Dave SP, Farooq U, Civantos FJ. Management of advanced laryngeal and hypopharyngeal plexiform neurofibroma in adults. American Journal of Otolaryngology - Head and Neck Medicine and Surgery 2008;29:279-283.	Irrelevant population
10	Farris SR, Grove AS, Jr. Orbital and eyelid manifestations of neurofibromatosis: a clinical study and literature review. Ophthalmic Plastic & Reconstructive Surgery 1996;12:245-59.	Irrelevant population
11	Fisher MJ, Shih CS, Rhodes SD, et al. Cabozantinib for neurofibromatosis type 1-related plexiform neurofibromas: a phase 2 trial. Nat Med 2021;27:165-173.	Irrelevant intervention
12	Freitas D, Aido R, Sousa M, et al. Carpal tunnel syndrome due to a plexiform neurofibroma of the median nerve in a neurofibromatosis type 1 patient: Clinical approach. BMJ Case Reports 2013;(no pagination).	Irrelevant population
13	Geoerger B, Moertel CL, Whitlock J, et al. Phase 1 trial of trametinib alone and in combination with dabrafenib in children and adolescents with relapsed solid tumors or neurofibromatosis type 1 (NF1) progressive plexiform neurofibromas (PN). Journal of Clinical Oncology 2018;36:10537-10537.	No relevant outcomes reported
14	Gupta A, Cohen BH, Ruggieri P, et al. Phase I study of thalidomide for the treatment of plexiform neurofibroma in neurofibromatosis 1. Neurology 2003;60:130-132.	Irrelevant intervention
15	Harris MC, Sorto LA. Plexiform neurofibroma: a case presentation. Journal of Foot Surgery 1981;20:124-6.	Irrelevant population

16	Hartley N, Rajesh A, Verma R, et al. Abdominal manifestations of neurofibromatosis. Journal of Computer Assisted Tomography 2008;32:4-8.	Irrelevant study design
17	Hua C, Zehou O, Ducassou S, et al. Sirolimus improves pain in NF1 patients with severe plexiform neurofibromas. Pediatrics 2014;133:Irrelevant study design792-Irrelevant study design797.	Irrelevant intervention
18	Karmazyn B, Cohen MD, Jennings SG, et al. Marrow signal changes observed in follow-up whole-body MRI studies in children and young adults with neurofibromatosis type 1 treated with imatinib mesylate (Gleevec) for plexiform neurofibromas. Pediatric Radiology 2012;42:1218-1222.	Irrelevant population
19	Kebudi R, Cakir FB, Gorgun O. Interferon-alpha for unresectable progressive and symptomatic plexiform neurofibromas. Journal of Pediatric Hematology/Oncology 2013;35:Irrelevant study design15-Irrelevant study design17.	Irrelevant intervention
20	Kim A, Dombi E, Tepas K, et al. Phase I trial and pharmacokinetic study of sorafenib in children with neurofibromatosis type I and plexiform neurofibromas. Pediatric Blood and Cancer 2013;60:396-401.	Irrelevant intervention
21	Kim A, Gillespie A, Dombi E, et al. Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas. Neurology 2009;73:1273-1279.	No relevant outcomes reported
22	Lastra RR, Bavuso N, Randall TC, et al. Neurofibroma of the cervix presenting as cervical stenosis in a patient with neurofibromatosis type 1: A case report. International Journal of Gynecological Pathology 2012;31:200-202.	Irrelevant population
23	Malhotra N, Levy JMS, Fiorillo L. Topical sirolimus as an effective treatment for a deep neurofibroma in a patient with neurofibromatosis type I. Pediatric Dermatology 2019;36:360-361.	Irrelevant population
24	McCowage GB, Mueller S, Pratilas CA, et al. Trametinib in pediatric patients with neurofibromatosis type 1 (NF-1)–associated plexiform neurofibroma: A phase I/IIa study. Journal of Clinical Oncology 2018;36:10504-10504.	Irrelevant intervention
25	Nct. Vitamin D Supplementation for Adults With Neurofibromatosis Type 1 (NF1). https://clinicaltrials.gov/show/NCT01968590 2013.	Irrelevant population
26	Niagolova S, Nachev R, Nikolova M, et al. A case of neurofibromatosis 1 presented with plexiform neurofibroma, neuroglial hamartoma and skin macules. [Bulgarian]. Rentgenologiya i Radiologiya 2005;44:218-221.	Irrelevant population
27	Nishitani M, Dolan P, Gundeti M, et al. Teen with Neurofibromatosis Type 1 Presents with Large Scrotal Mass and Large Tumor Burden. Pediatrics 2018;142:464.	Irrelevant population
28	Oruc M, Gursoy K, Yildiz K, et al. Giant plexiform neurofibroma of the upper limb and anterior chest wall: Case report and review of the literature. European Journal of Plastic Surgery 2015;38:323-326.	Irrelevant population
29	Pascoe HM, Antippa P, Irving L, et al. Rare manifestation of Neurofibromatosis type 1: A plexiform neurofibroma involving the mediastinum and lungs with endobronchial neurofibromata. Journal of Medical Imaging and Radiation Oncology 2019;63:76-78.	Irrelevant population
30	Perek-Polnik M, Filipek I, Dembowska-Baginska B, et al. [Children with neurofibroma type 1 treated in the Children's Memorial Health Institute]. Medycyna Wieku Rozwojowego 2006;10:699-709.	Irrelevant population
31	Perreault S, Larouche V, Tabori U, et al. A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with	Irrelevant population

	refractory tumor and activation of the MAPK/ERK pathway: TRAM-01. BMC Cancer 2019;19 (1) (no pagination).	
32	Romo C, Slobogean B, Blair L, et al. RARE-54. Mek Inhibition For Aggressive Gliomas In Adults With Neurofibromatosis Type 1. Neuro-Oncology 2019;21:vi233-vi233.	Irrelevant population
33	Serletis D, Parkin P, Bouffet E, et al. Massive plexiform neurofibromas in childhood: natural history and management issues. Journal of neurosurgery 2007;106:363-367.	Irrelevant intervention
34	Setyaningrum CTS. Transchateter arterial chemoinfusion (TACI) in patient with giant neurofibromatosis. Journal of the Neurological Sciences 2019;405:113.	Irrelevant population
35	Shih C-S, Blakely J, Clapp W, et al. NFM-01. NF105: A Phase Ii Prospective Study Of Cabozantinib (Xl184) For Plexiform Neurofibromas In Subjects With Neurofibromatosis Type 1: A Neurofibromatosis Clinical Trial Consortium (Nfctc) Study. Neuro-Oncology 2018;20:i142-i142.	Irrelevant population
36	Sirvaitis S, Sirvaitis R, Perusek T, et al. Early Cutaneous Signs of Neurofibromatosis Type 1. Journal of the Dermatology Nurses' Association 2017;9:191-193.	Irrelevant population
37	Slopis JM, Arevalo O, Bell CS, et al. Treatment of Disfiguring Cutaneous Lesions in Neurofibromatosis-1 with Everolimus: A Phase II, Open-Label, Single-Arm Trial. Drugs in R and D 2018;18:295-302.	Irrelevant population
38	Suarez Delgado JM, De la Matta Martin M. Anaesthetic implications of von recklinghausen's neurofibromatosis [1]. Paediatric Anaesthesia 2002;12:374.	Irrelevant population
39	Sun Q, Antaya RJ. Treatment of MEK inhibitor-induced paronychia with doxycycline. Pediatric Dermatology 2020;37:970-971.	Irrelevant population
40	Turkyilmaz Z, Sonmez K, Karabulut R, et al. A childhood case of intrascrotal neurofibroma with a brief review of the literature. Journal of Pediatric Surgery 2004;39:1261-1263.	Irrelevant population
41	Weiss B, Plotkin S, Widemann B, et al. NFM-06. NF106: Phase 2 Trial Of The Mek Inhibitor Pd-0325901 In Adolescents And Adults With Nf1-Related Plexiform Neurofibromas: An Nf Clinical Trials Consortium Study. Neuro-Oncology 2018;20:i143-i143.	Irrelevant population
42	Widemann BC, Salzer WL, Arceci RJ, et al. Phase I trial and pharmacokinetic study of the farnesyltransferase inhibitor tipifarnib in children with refractory solid tumors or neurofibromatosis type I and plexiform neurofibromas. Journal of Clinical Oncology 2006;24:507-516.	No relevant outcomes reported
43	Zhou L, Schalkwijk, S., Cohen-Rabbie, S., Jain, L., Freshwater, T., Tomkinson, H., Al-Huniti, N., Vishwanathan, K. and Zhou, D. Population pharmacokinetics and exposure-response of selumetinib and its N-desmethyl metabolite in pediatric patients with neurofibromatosis type-1 (NF-1) and inoperable plexiform neurofibromas (PN). Clinical Pharmacology & Therapeutics 2020;107:S96.	No relevant outcomes reported
44	Zugail AS, Benadiba S, Ferlicot S, et al. Oddities Sporadic Neurofibroma of the Urinary Bladder. A Case Report. Urology Case Reports 2017;14:42-44.	Irrelevant population

17.2 Appendix 2: Clinical SLR study extractions

Eight studies were identified in the SLR assessing the clinical efficacy of selumetinib. One of these studies was SPRINT Phase II Stratum I, which has been previously described in 9.3.1. One identified study, Kudek 2019, reported outcome data for patients receiving either selumetinib or trametinib.

Descriptions of the methodology, baseline characteristics, outcomes, and adverse events of the other seven studies identified can be found below.

Paediatric Populations

Baldo 2020

Table 10. Summary of methodology for Baldo 2020

Study name	Baldo 2020
Objective	To describe a prospective case series of patients treated with selumetinib with emphasis on drug adverse events
Location	Italy
Design	Interventional case-series (single-arm)
Duration of study	November 2017 to January 2020
Patient population	Paediatric patients with NF1 and inoperable PN
Sample size	9
Key inclusion criteria	• Patients with NF1 and inoperable PN • Patients who received selumetinib from November 2017 to January 2020
Key exclusion criteria	NR
Intervention(s) and comparator(s)	**Intervention:** Selumetinib BID; dosage between 20 mg/m^2 and 25 mg/m^2 **Comparator:** N/A
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were monitored with follow-up visits every 3 months. Direct phone communication was also established with the patient's parents and/or the patient themselves so that they could contact the clinician if they experienced any new AEs. MRI or CT scans were performed to assess the neurofibroma size 3 months after the beginning of treatment, and then every 6–9 months. The mean follow up was 12 months (range 3–26 months).
Statistical tests	All data were analysed using descriptive statistics
Outcomes (including scoring methods and timings of assessments)	• AEs Phone communication was established with patients/their parents to monitor possible AEs, in addition to a full clinical examination every 3 months comprising: a complete ophthalmological exam, a pneumological visit with a spirometry (if allowed by age and compliance of the patient), a cardiological visit with electrocardiogram and echocardiogram, and blood tests. • Tumour size in response to selumetinib

	MRI or CT scans were performed to assess the variation in size of the PN 3 months after treatment initiation; and then again every 6–9 months. The PN volume measurement and 3D evaluation were performed on axial scans with Horos™ by a radiologist with expertise in NF1 imaging evaluation. • Tumour reduction was defined as a mass shrinkage >20% • Tumour stabilisation was defined as a mass change between 0 and 20% • Tumour growth was defined as any expansion of the tumour at the end of the follow up

Abbreviations: AEs: adverse events; BID: twice daily; CT: computerized tomography; MRI: magnetic resonance imaging; N/A: not applicable; NF1: type 1 neurofibromatosis; PN: plexiform neurofibroma.
Source: Baldo 2020[117]

Table 11. Summary of patient baseline characteristics reported in Baldo 2020

Baseline characteristics, n	Baldo 2020 (N=9)
Number of patients	9
Number of PN	17
Age at start of treatment, years	
Mean	11
Range	4–18
Sex, n (%)	
Male	7 (78)
Female	2 (22)
Localisation of PN, n (%)[a]	
Head/neck	6 (35)
Chest/back	3 (18)
Abdomen/pelvis	3 (18)
Upper limbs	1 (6)
Lower limbs	4 (23)

Footnotes: [a]Number and percentage calculated from total number of PN.
Abbreviations: PN: plexiform neurofibroma.
Source: Baldo 2020[117]

Table 12. Summary of study outcomes reported in Baldo 2020

Outcome measure		Baldo 2020
Size of study groups	Treatment	Selumetinib
	Control	N/A
Study duration	Time unit	Mean follow-up 12 months (range 3–26)
Type of analysis	Intention-to-treat/per protocol	Intention-to-treat
Outcome	Name	Number of PN demonstrating growth in volume[a]
	Unit	n (%)
Effect size	Value	0 (0)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A

Outcome	**Name**	Number of PN demonstrating stabilisation in volume[a]
	Unit	n (%)
Effect size	**Value**	1 (6)
	95% CI	N/A
Statistical test	**Type**	N/A
	P value	N/A
Outcome	**Name**	Number of PN demonstrating reduction in volume[a]
	Unit	n (%)
Effect size	**Value**	16 (94)
	95% CI	N/A
Statistical test	**Type**	N/A
	P value	N/A
Outcome	**Name**	Number of patients with a clinical benefit reported since the beginning of the therapy
	Unit	n (%)
Effect size	**Value**	7 (78)
	95% CI	N/A
Statistical test	**Type**	N/A
	P value	N/A
Outcome	**Name**	The median size reduction of the PN to selumetinib
	Unit	%
Effect size	**Value**	23
	95% CI	N/A
Statistical test	**Type**	N/A
	P value	N/A
Outcome	**Name**	The range of radiological response to selumetinib
	Unit	%
Effect size	**Value**	14–57
	95% CI	N/A
Statistical test	**Type**	N/A
	P value	N/A

Footnote: aReported from the total number of PN across all patients; which is 17.
Abbreviations: CI: confidence interval; N/A: not applicable; PN: plexiform neurofibroma.
Source: Baldo 2020[117]

Table 13. Summary of general adverse events reported in Baldo 2020

AEs	Selumetinib (N=9)
All grade AEs, n (%)	NR[a]
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	1 (NR)

Treatment-emergent SAEs, n (%)	0 (0)
Deaths, n (%)	0 (0)
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	NR

Footnote: [a]Except for the one patient who experienced an SAE, all other AEs observed were minor.
Abbreviations: AE: adverse event; NR: not reported; SAE: serious adverse event.
Source: Baldo 2020[117]

Table 14. Summary of adverse events reported across patient groups in Baldo 2020

Adverse event	Intervention n (%) of patients (n = 9)
Acne	7 (78)
Paronychia	6 (67)
Diarrhoea	6 (67)
Irritability	4 (44)
Raised creatine kinase	2 (22)
Ischemic stroke	1 (11)
Mucositis	1 (11)
Sole desquamation	1 (11)
Adapted from European Public Assessment Reports published by the European Medicines Agency	

Source: Baldo 2020[117]

Table 15. Critical appraisal of Baldo 2020

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	The recruitment methods are NR.
Was the exposure accurately measured to minimise bias?	Yes	The minimum and maximum treatment doses are clearly stated.
Was the outcome accurately measured to minimise bias?	Yes	The AEs and tumour volumes were assessed by physicians and radiologists, respectively, with NF1 expertise. The patients were all from one location, which would minimise bias.
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.
Was the follow-up of patients complete?	Yes	The patients were followed up for a mean period of 12 months.
How precise (for example, in terms of	Not clear	Confidence intervals not stated; single-arm design means groups cannot be compared

confidence interval and p values) are the results?		
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: AEs: adverse events; N/A: not applicable; NR: not reported.
Source: Baldo 2020[117]

Espirito Santo 2020

Table 16. Summary of methodology for Espirito Santo 2020

Study name	Espirito Santo 2020
Objective	To describe the experience with selumetinib used in a single institution for the treatment of inoperable PN in NF1
Location	Portugal
Design	Case series
Duration of study	Mean follow-up: 223 days
Patient population	NF1 patients with inoperable PN associated with significant morbidity or potentially significant morbidity, aged 3–19 years
Sample size	19
Key inclusion criteria	• NF1 PN patients that fulfilled the criteria for selumetinib treatment: o Inoperable PN associated with significant or potentially significant morbidity o At least 6 months of follow up o MPNST exclusion after FDG-PET/CT scan o Normal laboratory results and cardiac function
Key exclusion criteria	• Asymptomatic PN • MPNST • Low performance status
Intervention(s) and comparator(s)	**Intervention:** Selumetinib 25 mg/m^2 BID **Comparator:** N/A
Baseline differences	**N/A**
How were participants followed-up (for example, through pro-active follow-up or passively). **Duration of follow-up, participants lost to follow-up**	Patients were followed-up monthly (physical examination, evaluation of treatment adherence and blood analysis), every 3 months (echocardiogram) and 6 months (MRI). Mean length of follow-up was 223 days (35–420 days). The number of patients lost to follow-up is not reported.
Statistical tests	Favourable response/PN shrinkage was defined as at least a 30% decrease in the sum of diameters of target lesions. Descriptive statistics include median, minimum and maximum values for continuous variables numbers while numbers and percentages of patients are presented for categorical variables.
Primary outcomes (including scoring	**Clinical improvement**

methods and timings of assessments)	For clinical evaluation, the single most trouble symptom in each patient was considered; a qualitative all or nothing response (visual inspection for disfigurement), and self-reported benefits (any improvement: yes/no, improvement of specific symptoms: yes/no). **PN size** Measured using MRI, a decrease in size was defined as at least a 30% decrease in the sum of diameters of target lesions. The RECIST criteria was used to assess tumour reduction. MRI assessment occurred every 6 months. **Safety** Adverse events were assessed using the CTCAE criteria. Physical examinations were carried out monthly.
Secondary outcomes (including scoring methods and timings of assessments)	NR[a]

Footnotes: [a]As outcomes have not been classified as primary or secondary, all have been extracted as primary outcomes

Abbreviations: BID: twice a day; CT: computerised tomography; CTCAE: Common Terminology Criteria for Adverse Events; FDG-PET: fluorodeoxyglucose-positron emission tomography; MPNST: malignant peripheral nerve sheath tumours; MRI: magnetic resonance imaging; N/A: not applicable; NF1: type 1 neurofibromatosis; NR: not reported; PN: plexiform neurofibroma; RECIST: Response evaluation in solid tumours.

Source: Espirito Santo 2020[127]

Table 17. Summary of patient baseline characteristics reported in Espirito Santo 2020

Disease characteristics	Espirito Santo 2019 (N=19)
Median age (range) at enrolment, years	13 (3–19)
Male, n	15
Female, n	4
Median PS score (range)	80 (50–90)
Target PN location, n	
Head and neck	6
Chest	5
Pelvis	5
Upper and lower limbs	3
Progression status of target PN at enrolment, n	
Progressive	8
Nonprogressive	11
Most important complication related to PN at baseline, n	
Disfigurement	8
Pain	5
Motor dysfunction	3
Urinary symptoms	4

Abbreviations: PN; plexiform neurofibroma; PS: performance status.

Source: Espirito Santo 2020[127]

Table 18. Summary of study outcomes for Espirito Santo 2020

Outcome measure		Espirito Santo 2020
Size of study groups	Treatment	19
	Control	Intention-to-treat
Study duration	Time unit	Mean follow-up: 223 days
Type of analysis	Intention-to-treat/per protocol	Intention-to-treat
Outcome	Name	Clinical improvement
	Unit	n/N
Effect size	Value	Nerve function improvement: 4/4; motor function improvement: 3/3; urinary incontinence resolution: 3/4; disfigurement improvement: 4/8
	95% CI	N/A
Statistical test	Type	NR
	P value	NR
Outcome	Name	PN size reduction
	Unit	n (%)
Effect size	Value	9 (47.3)
	95% CI	N/A
Statistical test	Type	NR
	P value	NR

Abbreviations: CI: confidence interval; N/A: not applicable; NR: not reported; PN: plexiform neurofibroma.
Source: Espirito Santo 2020[127]

Table 19. Summary of general adverse events for Espirito Santo 2020

AEs	Selumetinib (N=19)
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	2 (NR)
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	1 (NR)

Abbreviations: AE: adverse event; NR: not reported; SAE: serious adverse event.
Source: Espirito Santo 2020[127]

Table 20. Summary of adverse events reported in Espirito Santo 2020

	Mean follow-up: 223 days
	Intervention n of patients (n = 19)
Acneiform rash (Grade 2)	7
Asymptomatic left ventricular ejection fraction reduction (Grade 2)	4

Paronychia (Grade 2)	3
Nausea and vomiting (Grade 2)	1
Erythematous rash (Grade 2)	1
Neutrophil count decrease (Grade 2)	1
Asymptomatic CPK increase (Grade 3)	2

Abbreviations: CPK: creatine phosphokinase; N/A: not applicable.
Source: Espirito Santo 2020[127]

Table 21. Critical appraisal of Espirito Santo 2020

Espirito Santo 2020		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All NF1 patients treated at the institution during the study period were assessed for eligibility, no evidence of selection bias
Was the exposure accurately measured to minimise bias?	Yes	Intervention was described
Was the outcome accurately measured to minimise bias?	Yes	Measures are objective, however volumetric analysis was not used to assess PN size, which is the recommended measure used in clinical trials
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.
Was the follow-up of patients complete?	Yes	Mean follow-up was 223 days and no patients have been reported to have been lost to follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Outcomes are categorical (n or %). No confidence intervals or p values have been reported.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: N/A: not applicable; NF1: type 1 neurofibromatosis; PN: plexiform neurofibroma.
Source: Espirito Santo 2020[127]

SPRINT: Phase I

Table 22. Summary of methodology for SPRINT: Phase I

Study name	SPRINT: Phase I (NCT01362803)
Objective	To study the safety and effectiveness of selumetinib in children and young adults with PN that cannot be completely removed by surgery
Location	USA (four study centres)

Design	Interventional study (open-label, Phase I)
Duration of study	Patients enrolled from 21st September 2011 to 27th February 2014 Data cut-off 4th January 2016
Patient population	Children aged 3–18 years with inoperable, measurable PN associated with clinically diagnosed NF-1
Sample size	24
Key inclusion criteria	• Aged >3 and ≤18 years of age at the time of enrolment. • Diagnosis of NF1 with inoperable PN that have the potential to cause significant morbiditya • Positive genetic testing for NF1, or at least one of the NIH consensus diagnostic criteria additional to PN • At least one measurable PN, defined as a lesion of ≥3 cm measured in one direction • Karnofsky/Lansky PS ≥70% • Adequate hematologic function, defined as ANC ≥1000/µl, hemoglobin ≥9g/dl, and platelet ≥100,000/µl. . • Adequate hepatic function, defined as bilirubin within 1.5 x ULN for age, with the exception of Gilbert syndrome, and ALT within ≤ 1.5 x ULN • Adequate renal function, defined as CrCl or radioisotope GFR ≥60ml/min/1.73 m2, or normal serum creatinine based on age
Key exclusion criteria	• Pregnant or breast-feeding women • Patients who anticipate the need for surgical intervention within the first three cycles (3 months) • Use of an investigational agent within the past 30 days • Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumour, immunotherapy, or biologic therapy • Clinically significant, uncontrolled unrelated systemic illness such as serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction • Inability to undergo MRI or contraindication for MRI • Prior treatment with selumetinib or another MEK1/2 inhibitor (unless the subject meets criteria for re-treatment • Evidence of an OG, MG, MPNST, or other cancer requiring treatment with chemotherapy or radiation therapy
Intervention(s) and comparator(s)	**Intervention:** Selumetinib, 20–30 mg/m^2 BSA BID (n=24)[b] Patients received either 20 mg/m^2, 25 mg/m^2, 30mg/m^2 **Comparator:** N/A (single-arm trial)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Safety analyses were planned pre-study, prior to selumetinib cycles and at the end of therapy. Duration of follow-up and losses to follow-up not reported.
Statistical tests	Descriptive statistics (mean, SD, median and range)

Primary outcomes (including scoring methods and timings of assessments)	• MTD, defined as the highest dose level at which one third of the patients or fewer had dose-limiting toxic effects during cycles 1 to 3, and tolerability Adverse events were graded according to NCI CTCAE, v4.0 • Recommended phase II dose of selumetinib administered BID, 28 day cycles, no rest period Patient assessments included clinical examinations, laboratory evaluations, ophthalmologic examinations, echocardiography, and electrocardiography at baseline and at regular intervals during the trial.
Secondary outcomes (including scoring methods and timings of assessments)	• Effect of selumetinib on growth rate of PN using MRI (images obtained after cycles 5 and 10 and thereafter after every 6 cycles). A partial response was defined as a tumour volume decrease from baseline of ≥20% for ≥4 weeks. Disease progression was defined as a tumour volume increase from baseline of at least 20%. Stable disease was defined as a tumour volume change from baseline of less than 20%. • Pharmacodynamics in PBMCs by evaluating ERK phosphorylation • Plasma PK, measured by blood samples obtained on day 1 before the first dose of selumetinib was administered and 0.5, 1, 2, 3, 5, 8, 10 to 12, 24, and 30 to 36 hours after administration of that dose. In addition, a blood sample was obtained on day 27 before the first dose was administered • Dosing adherence, measured by Responsibility for Medication Questionnaire, patient diary review and capsule counts • Chronic dosing toxicity

Footnotes: aPatients were considered inoperable if complete tumour resection was not considered to be feasible without substantial risk or morbidity, or if a patient with a surgical option refuses surgery. bStarting dose was 20 mg/m2 BSA BID, with potential dose escalations to 50 mg/m2 BSA, a standard 3 + 3 phase 1 dose escalation design was followed.
Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; BID: twice daily; CrCl: creatinine clearance; CTCAE: Common Terminology Criteria for Adverse Events; ERK: extracellular signal-regulated kinase; GFR: glomerular filtration rate; MG: malignant glioma; MPNST: peripheral nerve sheath tumour; MRI: magnetic resonance imaging; MTD: maximum tolerated dose; N/A: not applicable; NCI: National Cancer Institute; NF-1: type 1 neurofibromatosis; NIH: National Institutes of Health; NR: not reported; OG: optic glioma; PBMC: peripheral blood mononuclear cells; PK: pharmacokinetics; PN: plexiform neurofibromas; PS: performance status; SD: standard deviation; ULN: upper limit of normal.
Source: Dombi 2016[39], ClinicalTrials.gov (NCT01362803)[67]

Table 23. Summary of patient baseline characteristics reported in SPRINT: Phase I

Disease characteristics	SPRINT: Phase I (N=24)
Median PS score (range)[a]	90 (70–100)
Median target PN volume, mL (range)	1,205 (29–8,744)
Demographics	
Median age at enrolment, years (range)	10.9 (3.0–18.5)
Male (n)	13
Female (n)	11
Previous medical interventions, n	
Previous medical interventions for treatment of PN	41
Patients who had previous medical interventions	19
Median previous medical interventions per patient (range)	2 (1–6)

Previous PN debulking surgeries, n	
Previous debulking surgery for PN	25
Patients who underwent previous debulking surgery for PN	11
Median previous debulking surgeries per patient (range)	1 (1–6)
Predominant target location of PN, n	
Face	4
Both head and neck	1
Both neck and chest	6
Trunk	4
Both trunk and extremity (upper or lower)	8
Whole body	1
Progression status of target PN at enrolment, n (%)	
Progressive	9 (38)
Nonprogressive	8 (33)
Insufficient information	7 (29)
PN-related complications at baseline, n (%)	
Disfigurement	18 (75)
Pain	13 (54)
Motor dysfunction	9 (38)
Vision loss	1 (4)

Footnotes: [a]Karnofsky performance status was assessed in patients who were older than 16 years of age, and Lansky performance status was assessed in patients who were 16 years of age or younger.
Abbreviations: PN; plexiform neurofibroma; PS; performance status.
Source: Dombi 2016[39]

Table 24. Summary of study outcomes in SPRINT: Phase I

Outcome measure		SPRINT: Phase I (N=24)		
Size of study groups	Treatment	24		
	Control	N/A		
Study duration	Time unit	NR		
Type of analysis	Intention-to-treat/per protocol	Intention-to-treat		
Primary outcome				
Outcome	Name	MTD		
	Unit	mg/m^2		
Effect size	Value	25		
	95% CI	N/A		
Statistical test	Type	N/A		
	P value	N/A		
Secondary outcomes		Selumetinib 20 mg/m^2 (n=12)	Selumetinib 25 mg/m^2 (n=6)	Selumetinib 30 mg/m^2 (n=6)
Outcome	Name	PR		
	Unit	Tumour volume decrease from baseline ≥20%, n (%)		

Effect size	**Value**	9 (75)	5 (83)	3 (50)
	95% CI	NR	NR	NR
Statistical test	**Type**	N/A	N/A	N/A
	P value	N/A	N/A	N/A
Outcome	**Name**	Best response		
	Unit	% volume change from baseline (median)		
Effect size	**Value**	-31	-34	-19
	Range	-6, -47	-16, -44	-13, -34
Statistical test	**Type**	N/A	N/A	N/A
	P value	N/A	N/A	N/A
Outcome	**Name**	Time to best response		
	Unit	Months (median)		
Effect size	**Value**	22	18	8
	Range	5–42	9–22	5–24
Statistical test	**Type**	N/A	N/A	N/A
	P value	N/A	N/A	N/A

Abbreviations: CI: confidence interval; MTD, maximum tolerated dose; N/A, not applicable; NR, not reported, PR, partial response.
Source: Dombi 2016[39]

Table 25. Summary of general adverse events in SPRINT: Phase I

AEs	SPRINT: Phase I (N=24)
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	1 (NR)

Abbreviations: AE: adverse event.
Source: Dombi 2016[39]

Table 26. Summary of specific adverse events in SPRINT: Phase I

Toxicity Grade CTCAE v4.0	Cycles 1–3[b]			Cycles ≥4		
	Selumetinib 20 mg/m^2 (n=12)[c]	Selumetinib 25 mg/m^2 (n=6)[d]	Selumetinib 30 mg/m^2 (n=6)[e]	Selumetinib 20 mg/m^2 (n=12)[c]	Selumetinib 25 mg/m^2 (n=6)[d]	Selumetinib 30 mg/m^2 (n=6)[e]
Gastrointestinal (grades 2; 3)						
Abdominal Pain	2; 0	0; 0	1; 0	1; 0	3; 0	0; 0
Diarrhea	4; 0	1; 0	1; 0	3; 1	1; 0	1; 0
Constipation	0; 0	0; 0	0; 0	1; 0	0; 0	0; 0
Nausea	2; 0	0; 0	0; 0	2; 0	0; 0	0; 0
Vomiting	1; 0	0; 0	0; 0	4; 0	0; 0	0; 0
Anorexia	0; 0	0; 0	0; 0	1; 0	0; 0	1; 0
Mucositis (Oral)	0; 0	0; 0	1; 0	0; 0	1; 0	0; 1
Gastroesophageal Reflux Disease	0; 0	0; 0	0; 0	1; 0	0; 0	0; 0
Dermatologic (grades 2; 3)						
Rash (Acneiform)	2; 0	1; 0	4; 0	1; 0	0; 0	2; 0
Rash (Maculopapular)	0; 0	0; 1	0; 0	0; 0	0; 0	2; 0
Pruritis	1; 0	2; 0	1; 0	1; 0	0; 0	0; 0
Dry Skin	0; 0	1; 0	0; 0	2; 0	0; 0	1; 0
Urticaria	0; 1	0; 0	0; 0	0; 0	0; 0	0; 0
Hepatic (grades 2; 3)						
AST ↑	0; 0	0; 0	0; 0	1; 0	0; 0	0; 0
Metabolic/laboratory (grades 2; 3; 4)						
CPK ↑	0; 0; 0	2; 0; 0	2; 1; 0	1; 1; 0	2; 0; 1	1; 2; 0
Albumin ↓	0; 0; 0	0; 0; 0	0; 0; 0	0; 0; 0	1; 0; 0	1; 0; 0
Phosphorus ↓	0; 0; 0	0; 0; 0	0; 0; 0	0; 0; 0	1; 0; 0	1; 0; 0
Potassium ↑	0; 0; 0	0; 0; 0	0; 0; 0	0; 0; 0	1; 0; 0	0; 0; 0
Constitutional (grades 2; 3)						
Fatigue	0; 0	0; 0	1; 0	0; 0	1; 0	1; 0
Fever	1; 0	0; 0	0; 0	0; 0	0; 0	0; 0

Hematologic (grades 2; 3)						
White Blood Cell ↓	0; 0	0; 0	0; 0	1; 0	0; 0	1; 0
Neutrophil Count ↓	0; 0	0; 0	1; 0	4; 0	0; 0	4; 0
Lymphocyte Count ↑	0; 0	0; 0	0; 0	1; 0	1; 0	1; 0
Neurologic (grades 2; 3)						
Headache	0; 0	0; 0	0; 0	0; 0	0; 0	2; 0
Pain (grades 2; 3)						
Non-cardiac chest pain	0; 0	0; 0	0; 0	1; 0	0; 0	0; 0
Pain (Other)	0; 0	0; 0	1; 0	0; 0	0; 0	0; 0
Musculoskeletal Toxicity (grades 2; 3)						
Myalgia	0; 0	0; 0	0; 0	0; 0	0; 0	1; 0
Renal/Genitourinary Toxicity (grades 2; 3)						
Creatinine ↑	2; 0	0; 0	0; 0	1; 0	0; 0	0; 0
Proteinuria	1; 0	0; 0	0; 0	0; 0	0; 0	0; 0
Haematuria	1; 0	0; 0	0; 0	0; 0	0; 0	0; 0
Urinary Tract Infection	1; 0	0; 0	0; 0	0; 0	0; 0	0; 0
Infection (grades 2; 3)						
Paronychia/Nail Infection	0; 0	0; 0	0; 0	2; 0	1; 0	1; 0
Skin Infection	0; 0	0; 0	0; 0	1; 1	0; 0	0; 0
Cellulitis	0; 1	0; 0	0; 0	0; 1	0; 0	0; 0
Cardiac (grades 2; 3)						
Hypertension	0; 0	1; 0	0; 0	0; 0	0; 0	0; 0
Ejection Fraction ↓	0; 0	0; 0	0; 0	2; 0	0; 0	2; 1
Adapted from European Public Assessment Reports published by the European Medicines Agency						

Footnote: aAEs ≥grade 2 in severity listed in this table; full counts including grade 1 AEs are given in Dombi 2016 (Table S4). bDuring cycles 1–3, the mean percentage of patients who were considered to have adhered to the dosing schedule was 99% (range, 91–100) on the basis of patient diaries and 98% (range 96–100) on the basis of capsule counts. Patients (n=24) received a median of 30 cycles of selumetinib (range, 6–56), all dose-limiting toxic effects were reversible cPatients (n=12) received a median of 30 cycles of selumetinib (range, 6–56), doses were reduced as a result of dose-limiting toxic effects for 4/12 patients dPatients (n=6) received a median of 25 cycles of selumetinib (range, 23–26), doses were reduced as a result of dose-limiting toxic effects for 3/6 patients ePatients (n=6) received a median of 32 cycles of selumetinib (range, 18–40), doses were reduced as a result of dose-limiting toxic effects for 4/6 patients.

Abbreviations: AST: Aspartate Aminotransferase; CPK: creatine phosphokinase; CTCAE: Common Terminology Criteria for Adverse Events

Source: Dombi 2016[39]

Table 27. Critical appraisal of SPRINT: Phase I

SPRINT: Phase I		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	The patient recruitment is not reported, however the study spans 4 treatment centers across the USA
Was the exposure accurately measured to minimise bias?	Yes	The treatment dosing is clearly reported
Was the outcome accurately measured to minimise bias?	Yes	Outcome measures and definitions are clearly stated, AEs are reported according to the NCI CTCAE, v4.0
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.
Was the follow-up of patients complete?	Not clear	It is not reported whether follow-up was complete
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Only descriptive statistics were used in this study, no CIs or p values are reported
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: AEs: adverse events; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; N/A: not applicable; NCI: National Cancer Institute.
Source: Dombi 2016[39], ClinicalTrials.gov (NCT01362803)[67]

SPRINT: Phase II, Stratum II

Table 28. Summary of methodology for SPRINT: Phase II, Stratum II

Study name	SPRINT Phase II (NCT01362803)[redacted]
Objectives	To characterise the effect of selumetinib in patients without clinically significant baseline PN-related morbidity and determine if PN related morbidity developed during the course of treatment
Location	US (four study centres)
Design	Interventional study (open-label, Phase II)
Duration of study	Trial ongoing
Patient population	Stratum II: Children and young adults, aged 2–18 years, with NF1 and PN, with no significant PN related morbidity present at enrolment, but potential to develop PN morbidity
Sample size	25
Key inclusion criteria	• Aged 2–18 years • BSA ≥0.55 m^2 • Able to swallow whole capsules Diagnosis of NF1: • Positive genetic testing for NF1, or • At least one of the NIH consensus diagnostic criteria additional to PN Inoperable, symptomatic PN: • PN were required to be measurable, defined as a lesion of at least 3 cm, measured in one dimension • A PN was defined as inoperable if it could not be surgically completely removed without risk of substantial morbidity due to encasement or close proximity to vital structures, invasiveness or high vascularity • Patients who had previously undergone surgery for a PN were eligible provided the PN was not completely resected and was still measurable • Significant morbidity included (but was not limited to) deformity or disfigurement, limb hypertrophy or loss of function, pain, airway or great vessel compromisation, or nerve compression in the regions of the brachial or lumbar plexus
Key exclusion criteria	• Use of any investigational agent within the previous 30 days • Patients with ongoing radiation therapy, chemotherapy or hormonal therapy directed at the tumour, immunotherapy or biologic therapy • Inability to undergo MRI or contraindication for MRI examinations • Prior treatment with selumetinib or another MEK1/2-specific inhibitor, unless the subject meets criteria for re-treatment

	• Evidence of an optic glioma, malignant glioma, MPNST or other cancer requiring treatment with chemotherapy or radiation therapy
Intervention (n=25) and comparator	**Intervention:** Selumetinib 25 mg/m^2 BSA BID **Comparator:** N/A (single-arm trial)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Efficacy outcomes were assessed after one-year of treatment Long-term safety follow-up was planned for a duration of seven years from the initiation of treatment, or five years after completion of selumetinib treatment, whichever takes longer. Follow-ups included an annual health check and safety evaluations.
Statistical tests	With 75 patients in the overall population (Strata I and II), 19 or more responses in these 75 patients (response rate of ≥25%) would be associated with a lower bound of a two-sided 95% CI exceeding 15.0%
Primary outcomes (including scoring methods and timings of assessments)	See SPRINT: Phase II, Stratum 1 in Section 9.3.1. PR and CR rate of selumetinib in all patients with (Stratum I) and without (Stratum II) PN-related morbidity at the time of enrolment, and separate PR and CR rate for patients in Stratum II, was recorded **Morbidity:** Patients were evaluated to determine the presence of potential clinically relevant PN-related morbidities at baseline and follow-up visits
Secondary outcomes (including scoring methods and timings of assessments)	NR

Abbreviations: BID: twice daily; BSA: body surface area; CI: confidence interval; CR: complete response; MPNST: malignant peripheral nerve sheath tumour; NF1: type 1 neurofibromatosis ; NIH: National Institutes of Health; PN: plexiform neurofibromas; PR: partial response.
Source: AstraZeneca Data on File (CSR)[34]; Gross 2020[18], ClinicalTrials.gov (NCT01362803)[67], Glassberg 2020b[68]

Table 29. Summary of patient baseline characteristics reported in SPRINT: Phase II, Stratum II

Disease characteristics	SPRINT: Phase II Stratum 2 (N=25)
Median baseline tumour volume, mL (range)	381 (12–3,159)
Progressive PN growth at baseline,[a] n	11
Functional evaluations within normal limits[b]	
Strength, n	12
ROM, n	8
Exophthalmometry, n	2
Pulmonary function, n	8
Demographics	
Median age at baseline, years (range)	12.3 (4.5–18.1)
Male, %	64

Footnotes: [a]≥20% increase in PN volume within 15 months prior to enrolment [b]Excluding patients with non-PN related comorbidities limiting their functional status (e.g. scoliosis)

Abbreviations: PN: plexiform neurofibroma; ROM: range of motion.
Source: Glassberg 2020b[68]

Table 30. Summary of study outcomes for SPRINT: Phase II, Stratum II

Outcome measure		SPRINT: Phase II Stratum 2 (N=25)
Size of study groups	Treatment	25
	Control	N/A
Study duration	Time unit	Outcomes measured after 12 treatment cycles (28 days each)
Type of analysis	Intention-to-treat/per protocol	NR
Outcome	Name	PN volume decrease
	Unit	Median, %
Effect size	Value	29%
	Range	2.5%–37.9%
Statistical test	Type	NR
	P value	NR
Outcome	Name	PR
	Unit	Tumour volume shrinkage from baseline ≥20%, n (%)
Effect size	Value	18 (72)
	95% CI	NR
Statistical test	Type	NR
	P value	NR
Outcome	Name	Functional evaluation
	Unit	NA
Effect size	Value	No statistically significant changes (improvement or worsening) in strength, ROM, exophthalmometry, or pulmonary function
	95% CI	NR
Statistical test	Type	NR
	P value	>0.05

Abbreviations: CI: confidence interval: N/A: not applicable; NR: not reported; PN: plexiform neurofibroma; PR: partial response; ROM: range of motion.
Source: Glassberg 2020b[68]

Table 31. Summary of general adverse events for SPRINT: Phase II, Stratum II

AEs	SPRINT: Phase I (N=24)
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	3 (NR)
Discontinuations due to AEs[a], n (%)	1 (NR)

Footnote: [a]Asymptomatic elevation of lipase
Abbreviations: AE, adverse event
Source: Glassberg 2020b[68]

Table 32. Summary of adverse events reported across patient groups for SPRINT: Phase II, Stratum II

	SPRINT: Phase II stratum II
	Intervention % of patients (n = 25)
Asymptomatic lipase elevation	4%
Adapted from European Public Assessment Reports published by the European Medicines Agency	

Source: Glassberg 2020b[68]

Table 33. Critical appraisal of SPRINT: Phase II, Stratum II

SPRINT: Phase II Stratum 2		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients were recruited from 4 study sites across the US.
Was the exposure accurately measured to minimise bias?	Yes	The dose is clearly reported.
Was the outcome accurately measured to minimise bias?	Yes	The outcomes are objective.
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.

Was the follow-up of patients complete?	N/A	The study is ongoing.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values have been given to two decimal places.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Source: ClinicalTrials.gov (NCT01362803)[67], Glassberg 2020a[128], Glassberg 2020b[68]

Pooled Analysis: SPRINT: Phase II, Stratum I and II

Table 34. Summary of patient baseline characteristics reported in SPRINT: Phase II, Stratum I and II

Demographics	SPRINT: Phase II Stratum I and II (N=69)[a]
Median age at baseline (years), range	3.5–18.1

Footnotes: [a]SPRINT enrolled paediatric patients who had NF1 with inoperable PN, the study population was divided into two strata; those with (Stratum I) and without (Stratum II) PN-related morbidity at the time of enrolment. The records of all patients enrolled on study between August 2015 and November 2017 were reviewed. All patients received selumetinib (25 mg/m^2 BID)
Source: Pichard 2018[129]

Table 35. Summary of general adverse events in SPRINT: Phase II, Stratum I and II

AEs	SPRINT: Phase II Stratum 1 and 2 (N=69)[a]
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	NR
Patients experiencing cAEs, n	65
Individual cAEs, n	372
Grade 1/2 cAEs, n (%)[b]	360 (97)
Grade 3 cAEs, n (%)	11 (3)
Grade 4 cAEs, n (%)	1 (<1)

Footnote: [a]Patients received a median of 20 cycles of selumetinib (range 1–29) with one cycle lasting 28 days. [b]These resulted in no changes to selumetinib dose or course
Abbreviations: cAE: cutaneous adverse event.
Source: Pichard 2018[129]

Table 36. Summary of adverse events reported across patient groups SPRINT: Phase II, Stratum I and II

	Selumetinib 25 mg/m^2 BID, % of patients (N=69)	n (%) of all cAEs (n=372)
Acneiform eruption	52[a]	80 (22)
Paronychia	35[b]	76 (20)
Eczema, xerosis, folliculitis, pigmentary dilution, hair thinning, mucositis[c]	NR	NR

Footnote: [a]First occurred early in treatment (median cycle 3, range 1–20), acneiform management included topical or oral antimicrobial drugs and topical corticosteroids. [b]First occurred later in treatment (median cycle 13, range 1–25), paronychia resulted in the highest number of drug interruption or dose reduction (n=7), management initially involved soaks, topical antimicrobials, oral antibiotics if necessary, and surgical management when refractory. [c]Occured less frequently, n(%) NR
Abbreviations: BID: twice daily; cAE: cutaneous adverse event; NR: not reported.
Source: Pichard 2018[129]

Pooled Analysis: SPRINT: Phase I and II

Table 37. Summary of patient baseline characteristics reported in SPRINT: Phase I and II

Demographics	SPRINT: Phase I and II (N=99)
Median age, years (range)	10.6 (3.0–18.5)

Source: Dombi 2020[126]

Table 38. Summary of study outcomes SPRINT: Phase I and II

Outcome measure		SPRINT: Phase I and II (N=99)[a]
Size of study groups	Treatment	99
	Control	N/A
Study duration	Time unit	Median (range) duration of treatment 38.9 (1.0–85.1) months
Type of analysis	Intention-to-treat/per protocol	NR
Outcomes		
Outcome	Name	PR
	Unit	≥20% volume increase above BR, n (%)
Effect size	Value	73 (74)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Stable disease
	Unit	n
Effect size	Value	25
	95% CI	N/A

Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Patients who achieved PR were slightly younger than those who did not (median age at enrollment 9.5 vs. 13.3 years)[b]
	Unit	N/A
Effect size	Value	N/A
	95% CI	N/A
Statistical test	Type	NR
	P value	0.01
Patients achieving PR (n=73)		
Outcome	Name	Time for PR to be observed
	Unit	Cycles, median (range)
Effect size	Value	8 (4–28)
	95% CI	NR
Statistical test	Type	NR
	P value	NR
Outcome	Name	Time for PR to be observed
	Unit	Months, median (range)
Effect size	Value	6.9 (3.2–25.9)
	95% CI	NR
Statistical test	Type	NR
	P value	NR
Outcome	Name	Time further shrinkage was observed from initial PR to best response
	Unit	Months, median (range)
Effect size	Value	14.1 (0–57.9)
	95% CI	NR
Statistical test	Type	NR
	P value	NR
Outcome	Name	Progressive disease after PR
	Unit	Patients requiring a dose reduction, n/N (%); patients not requiring a dose reduction, n/N (%)
Effect size	Value	10/18 (55.6); 12/55 (21.8)
	95% CI	NR
Statistical test	Type	NR
	P value	0.0156

Footnotes: [a]One patient had no response data. [b]Younger age was weakly correlated with more PN shrinkage at best response in the entire cohort (p=0.01); age did not have a significant effect on the degree of maximal PN shrinkage in the subset with PR (p=0.23)
Abbreviations: BR: best response; CI: confidence interval; N/A: not applicable; NR: not reported; PR: partial response.
Source: Dombi 2020[126]

Kudek 2019

Table 39. Summary of methodology for Kudek 2019

Study name	Kudek 2019
Objective	To implement a protocolised screening and treatment plan to safely prescribe MEKi to paediatric patients with NF1 and inoperable PN
Location	US
Design	Interventional, case report
Duration of study	Study is ongoing
Patient population	Paediatric patients with NF1 and inoperable PN
Sample size	3
Key inclusion criteria	• Patients who are ineligible for therapeutic clinical trial • Patients with significant morbidity from PN
Key exclusion criteria	• NR
Intervention(s) and comparator(s)	**Intervention:** Selumetinib tablets 25 mg/m^2 BID or trametinib suspension 0.025 mg/kg/d (maximum 2 mg). **Comparator:** N/A
Baseline differences	**N/A**
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Screening surveillance studies are performed prior to enrolment and prior to each monthly cycle. Patients were followed prospectively; ongoing length of treatment ranged from 2–6 months
Statistical tests	NR
Outcomes (including scoring methods and timings of assessments)	**Disease progression:** The methods of assessing disease progression are NR. Disease evaluation is scheduled for 6 and 12 months, then annually after this. **Clinical safety:** The following tests are scheduled to be performed prior to enrolment (month 1), month 2 and 3; then every 3 months. • Serum chemistries • Creatine kinase • Complete blood counts The following tests are scheduled prior to enrolment (month 1), months 3, 6 and 12; then at least annually. • Vision exam • ECG Complete dermatologic evaluation will be performed as needed, but at least annually.

Abbreviations: BID: twice a day; ECG: electrocardiogram; MEKi: MEK inhibitor; N/A: not applicable; NF1: type 1 neurofibromatosis; NR: not reported; PN: plexiform neurofibroma.
Source: Kudek 2019[135]

Table 40. Summary of patient baseline characteristics reported in Kudek 2019

Baseline characteristics	Kudek 2019 (N=3)
Selumetinib tablet patients, n	2
Trametinib suspension patients, n	1
Selumetinib patients ages, years	5 and 10
Trametinib patient age, years	6

Source: Kudek 2019[135]

Table 41. Summary of study outcomes in Kudek 2019

Outcome measure		Kudek 2019 (N=3)
Size of study groups	Treatment	Selumetinib or Trametinib
	Control	N/A
Study duration	Time unit	NR
Type of analysis	Intention-to-treat/per protocol	Per protocol
Outcome	Name	Progressive disease-related morbidity
	Unit	n
Effect size	Value	0
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A

Abbreviations: N/A: not applicable; NR: not reported.
Source: Kudek 2019[135]

Table 42. Summary of general adverse events in Kudek 2019

AEs	Kudek 2019 (N=3) Selumetinib (n=2) or trametinib (n=1)
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	NR

Footnotes: aPer CTCAE criteria
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event.
Source: Kudek 2019[135]

Table 43. Critical appraisal of Kudek 2019

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?

Was the cohort recruited in an acceptable way?	Not clear	The recruitment methods are NR
Was the exposure accurately measured to minimise bias?	Yes	The doses are clearly reported
Was the outcome accurately measured to minimise bias?	Not clear	It is not clear what methods were used to measure the outcomes
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.
Was the follow-up of patients complete?	N/A	The study is ongoing
How precise (for example, in terms of confidence interval and p values) are the results?	Not clear	There are no statistics reported in this study
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: N/A: not applicable; NR: not reported.
Source: Kudek 2019[135]

Pooled Analysis, SPRINT and NCT02407405

Table 44. Summary of patient baseline characteristics reported in SPRINT and NCT02407405

Baseline characteristics	SPRINT; NCT02407405 (N=24)
Age, years median (range)	16.9 (6.2–60.3)
Male, n	18
Female, n	6
History of surgical decompression, n	11
Median (range) PN volume, mL	890 (138–4444)
SNF location in relation to target PN location, n	
Same	22
Other	2
SNF distribution, n	
Multilevel symmetrical	13
Multilevel one-sided	8
Single nerve root	3
None	7

Bony spine deformity, n	
Kyphosis/scoliosis	9
Vertebral scalloping	8
Spinal stenosis	3
Vertebral erosion	1
Spinal instrumentation, n	
Fusion/stabilisation	5
Scoliosis repair	1
Target PN location, n	
Cervical/brachial plexus distribution	14
Lumbosacral plexus distribution	6
Whole body	4

Abbreviations: PN: plexiform neurofibroma.
Source: Jackson 2020[123]

Table 45. Summary of study outcomes SPRINT and NCT02407405

Outcome measure		SPRINT; NCT02407405
Size of study groups	Treatment	24
	Control	N/A
Study duration	Time unit	1st August 2015–31st October 2019
Type of analysis	Intention-to-treat/per protocol	NR
Outcome	Name	Degree of overall imaging improvement, rated on a subjective scale
	Unit	n (%)
Effect size	Value	Subtle improvement: 10 (43), marked improvement: 8 (35), no improvement: 5 (22)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Resolved spinal canal distortion[a]
	Unit	n
Effect size	Value	1
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Disruption of circumferential CSF[a]
	Unit	n
Effect size	Value	19 present at baseline, at cycle 12 4 had resolved, 13 had improved and 2 had no change
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Spinal cord deformity[a]
	Unit	n
Effect size	Value	19 present at baseline, at 12 cycles 1 had resolved, 9 had improved and 9 had no change
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A

Footnotes: aOut of a total of 23 evaluable patients
Abbreviations: N/A: not applicable, SNF: spinal neurofibroma.
Source: Jackson 2020[123], Jackson 2018b[125]

Table 46. Summary of general adverse events in SPRINT and NCT02407405

AEs	SPRINT; NCT02407405
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	NR

Abbreviations: NR: not reported.
Source: Jackson 2018a[124], Jackson 2018b[125], Jackson 2020[123]

Table 47. Summary of adverse events reported across patient groups

Adverse event	Intervention % of patients (n = 24)
NR	NR

Abbreviations: CI: confidence interval; N/A: not applicable; NR: not reported.

Adult Populations

NCT02407405

Table 48. Summary of methodology of NCT02407405

Study name	NCT02407405
Objective	To investigate the efficacy and safety of selumetinib for the treatment of inoperable PN
Location	US
Design	Interventional (open-label, Phase II)
Duration of study	Trial is ongoing
Patient population	Adult patients (≥18 years) with NF1, inoperable PN and ≥1 PN-related morbidity
Sample size	N=27
Key inclusion criteria	• Aged ≥18 years • ECOG PS ≤2 • Normal organ and marrow function Diagnosis of NF1: • Positive genetic testing for NF1 or a diagnosis based on clinical NIH consensus of at least one of the NIH consensus diagnostic criteria additional to PN Inoperable PN: • PN were required to be measurable, defined as a lesion of at least three cm, measured in one direction • A PN was defined as inoperable if it could not be surgically completely removed without risk of substantial morbidity due to encasement or close proximity to vital structures, invasiveness or

	high vascularity o Patients who had previously undergone surgery for a PN were eligible provided the PN was not completely resected and was still measurable • PN must be amenable to biopsy
Key exclusion criteria	• Use of any investigational agents within the previous 30 days • May not have a NF1 related tumour such as optic pathway glioma or malignant peripheral nerve sheath tumour, which requires treatment with chemotherapy or surgery • Uncontrolled intercurrent illness • Inability to undergo MRI or contraindication for MRI • Prior treatment with selumetinib or another MEK 1/2-specific inhibitor
Intervention(s) and comparator(s)	**Intervention:** Selumetinib 25 mg twice daily on a continuous dosing schedule of 28-day cycles (n=23) First two patients received 75 mg dose **Comparator:** N/A (single-arm trial)
Baseline differences	**N/A**
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Details on follow-up have not been reported. The outcomes have been reported for 21 patients with a minimum time on study of 1 year. With a data cut-off of February 2020, outcomes are reported for 23 patients.
Statistical tests	The overall target RR was 45% (method of calculation not reported). Descriptive statistics include median, minimum and maximum values for continuous variables and numbers while numbers and percentages of patients are presented for categorical variables. The statistical test used to calculate the significance of PROs has not been reported. The FAS included patients with a minimum time on study of 1 year.
Primary outcomes (including scoring methods and timings of assessments)	• Partial RR of PN, with a PR being defined as a ≥20% volume decrease, using volumetric MRI analysis • Complete RR of PN, with a CR not being defined, using volumetric MRI analysis Outcomes were assessed at baseline and after 1-year of treatment
Secondary outcomes (including scoring methods and timings of assessments)	• Pharmacodynamic studies of pre- and on-treatment biopsies of PN and cNF, assessing phospho-ERK/phospho-NEK levels from total cell lysates • Assessment of clinical benefit, assessed using the PRO measures NRS-11, PII, PedsQL-NF scale, and GIC Outcomes were assessed at baseline and after 1-year of treatment PRO measures were assessed at baseline, then after 4, 8, and 12 cycles (1 cycle=28 days)

Abbreviations: cNF: cutaneous neurofibromas; CR: complete response; FAS: full analysis set; GIC: Global Impression of Change; MRI: magnetic resonance imaging; N/A: not applicable; NF1: type 1 neurofibromatosis; NRS-11: Numeric Rating Scale-11; PedsQL: Pediatric Quality of Life Neurofibromatosis Scale; PII: Pain Interference Index; PN: plexiform neurofibroma; PRO: patient reported outcome; RR: response rate.

Source: Coyne 2020a[120]; Coyne 2020b[121]; Martin 2019[122]; Coyne 2019[118]; ClinicalTrials.gov (NCT02407405)[119]

Table 49. Summary of patient baseline characteristics reported in NCT02407405

Patient characteristics	NCT02407405 (N=23)
Male, %	74
Median age, years	33
Age range, years	18–60
PN-related morbidities, n	
Motor weakness *(N=21)*	13
Disfigurement	13
Pain	19
Motor dysfunction	17
NF1 severity[a]	
Severe, %	41
NF1 visibility[a]	
Severe, %	11.8
NRS-11 score	
Mean score (SD)	5.5 (3.4)
PII score	
Mean score (SD)	2.9 (1.5)

Footnotes:[a] Self-reported
Abbreviations: NF1: type 1 neurofibromatosis; NRS-11: Numeric Rating Scale-11; PII: Pain Interference Index; PN: plexiform neurofibroma; SD: standard deviation.
Source: Coyne 2020a[120]; Coyne 2020b[121]; Martin 2019[122]; Coyne 2019[118]

Table 50. Summary of study outcomes in NCT02407405

Outcome measure		NCT02407405 (N=23)
Size of study groups	Treatment	23
	Control	N/A
Study duration	Time unit	Patients enrolled on trial for a minimum of one year
Type of analysis	Intention-to-treat/per protocol	Intent-to-treat
Primary outcome		
Outcome	Name	Partial response rate
	Unit	n (%)
Effect size	Value	16 (69)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Secondary outcomes		
Outcome	Name	No disease progression rate
	Unit	n (%)
Effect size	Value	13 (57)

	95% CI	NR
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Median (range) change in PN volume
	Unit	%
Effect size	Value	-22 (-41–+5.5)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Median (range) time to response (data cut off February 2020)
	Unit	months
Effect size	Value	11 (5–25)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	Median (range) time to confirmed PR
	Unit	Months
Effect size	Value	14 (8–30)
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A
Outcome	Name	NRS-11 ratings at cycle 12, assessed in 17 patients
	Unit	Mean (SD) score
Effect size	Value, n=17	3.6 (3.3)
	95% CI	N/A
Statistical test	Type	NR
	P value	<0.05 (p vs. baseline)
Outcome	Name	PII ratings at cycle 12, assessed in 17 patients
	Unit	Mean (SD) score
Effect size	Value, n=17	1.5 (1.6)
	95% CI	N/A
Statistical test	Type	NR
	P value	<0.001 (p vs. baseline)

Abbreviations: N/A: not applicable; NR: not reported; NRS-11: Numeric Rating Scale-11; PII: Pain Interference Index; PN: plexiform neurofibroma; PR: partial response; SD: standard deviation; vs: versus.

Source: Coyne 2020a[120]; Coyne 2020b[121]; Martin 2019[122]; Coyne 2019[118]

Table 51. Summary of general adverse events in NCT02407405

AEs	Selumetinib (N=21)
All grade AEs, n (%)	NR
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	4 (NR)
Discontinuations due to AEs, n (%)	1 (NR)

Abbreviations: AEs: adverse event; NR: not reported; SAE: serious adverse event.
Source: Coyne 2020a[120]; Coyne 2020b[121]; Coyne 2019[118]

Table 52. Summary of adverse events reported across patient groups

	One year
	Intervention % of patients (n = 21)
Grade ≥3 AEs	
Transaminitis	23%
Rash	19%
Pancreatic enzyme elevation	19%

Abbreviations: AE: adverse event; CI: confidence interval; NA: not applicable.
Source: Coyne 2020a[120]; Coyne 2020b[121]; Martin 2019[122]; Coyne 2019[118]

Table 53. Critical appraisal of NCT02407405

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	Not enough information in the publications to determine recruitment methods
Was the exposure accurately measured to minimise bias?	Yes	All patients received the same intervention, regimen was well described
Was the outcome accurately measured to minimise bias?	Yes	Outcome measures are objective and therefore have a low risk of bias
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.

Was the follow-up of patients complete?	Not clear	No details on follow-up length or completeness, however only conference publications available
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P value reported to three decimal places
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: N/A: not applicable.
Source: Coyne 2020a[120]; Coyne 2020b[121]; Martin 2019[122]; Coyne 2019[118]

Case Study

Passos 2020

Table 54. Summary of methodology of Passos 2020

Study name	Passos 2020
Objective	To report the treatment of a 14-year-old male NF1 PN patient with selumetinib
Location	Portugal
Design	Interventional case-study
Duration of study	NR
Patient population	14-year-old male NF1 PN patient
Sample size	1
Key inclusion criteria	N/A
Key exclusion criteria	N/A
Intervention(s) and comparator(s)	**Intervention:** Selumetinib 35 mg every 12 hours orally for the first 14 months, then increased to 40 mg BID **Comparator:** N/A
Baseline differences	**N/A**
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	The follow-up methods are NR; however, he was treated for at least 15 months and follow-up data is available for 12 weeks and 6 months post treatment
Statistical tests	NR
Outcomes (including scoring methods and timings of assessments)	**Performance Status:** Lansky Performance Score This was measured at baseline and after 6 months of treatment Toxicities The timelines and assessment methods of toxicities are not reported.

Abbreviations: BID: twice a day; N/A: not applicable; NF1: neurofibromatosis type 1; NR: not reported; PN: plexiform neurofibroma.
Source: Passos 2020[136]

Table 55. Summary of patient baseline characteristics reported in Passos 2020

Baseline characteristics	Passos 2020 (N=1)
Age, years	14
Sex	Male
Lansky Performance Scale score	50
PN location	Buttocks, thighs and legs

Abbreviations: PN: plexiform neurofibroma.
Source: Passos 2020[136]

Table 56. Summary of study outcomes in Passos 2020

Outcome measure		Passos 2020
Size of study groups	Treatment	1
	Control	N/A
Study duration	Time unit	NR
Type of analysis	Intention-to-treat/per protocol	Intent-to-treat
Outcome	Name	Lansky Performance Scale after 6 months of treatment
	Unit	N/A
Effect size	Value	80
	95% CI	N/A
Statistical test	Type	N/A
	P value	N/A

Abbreviations: CI: confidence interval; N/A: not applicable; NR: not reported; PN: plexiform neurofibroma.
Source: Passos 2020[136]

Table 57. Summary of general adverse events in Passos 2020

AEs	Selumetinib (N=1)
All grade AEs, n (%)	1 (100)
Grade ≥3 AEs, n (%)	NR
Treatment-emergent grade ≥3 AEs, n (%)	NR
SAEs, n (%)	NR
Treatment-emergent SAEs, n (%)	NR
Deaths, n (%)	NR
Dose interruptions due to AEs, n (%)	NR
Dose reductions due to AEs, n (%)	NR
Discontinuations due to AEs, n (%)	NR

Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Passos 2020[136]

Table 58. Summary of adverse events reported across patient groups in Passos 2020

	Intervention n (%) of patients (n = 1)
Asymptomatic creatine phosphokinase increase of >5 times normal upper limit	100%
Asymptomatic pericardial effusion	100%

Adapted from European Public Assessment Reports published by the European Medicines Agency
Abbreviations: CI, confidence interval
Source: Passos 2020[136]

Table 59. Critical appraisal of Passos 2020

Passos 2020		
Study question	**Response**	**How is the question addressed in the study?**

	yes/no/not clear/N/A)	
Was the cohort recruited in an acceptable way?	N/A	Case-study
Was the exposure accurately measured to minimise bias?	Yes	The dose of treatment is clearly stated
Was the outcome accurately measured to minimise bias?	Not clear	The measurements of outcomes are not reported; except for performance status which is measured using a validated measure
Have the authors identified all important confounding factors?	N/A	This is a single-arm study.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	This is a single-arm study.
Was the follow-up of patients complete?	Yes	The follow-up methods are NR; however, he was treated for at least 15 months and follow-up data is available for 12 weeks and 6 months post treatment
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	No formal statistics used
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: N/A: not applicable; NR: not reported.
Source: Passos 2020[136]

17.3 Appendix 3: Search strategy for adverse events

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The search for clinical evidence included identifying any adverse events reported for selumetinib and other emerging therapies for NF1 with PN. For databases searched refer to Section 17.1.1.

17.3.2 The date on which the search was conducted.

See the clinical evidence search in Section 17.1.2.

17.3.3 The date span of the search.

See the clinical evidence search in Section 17.1.3.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See the clinical evidence search in Section 17.1.4.

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See the clinical evidence search in Section 17.1.5.

17.3.6 The inclusion and exclusion criteria.

See Table C1 in Section 9.1.1.

17.3.7 The data abstraction strategy.

See the clinical evidence search in Section 17.1.7.

17.4 Appendix 4: Search strategy for economic evidence

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Electronic Databases

- The following electronic databases were searched:
    - Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (searched via the Ovid SP platform, from 1946 to January 25, 2021)
    - Embase (searched via the Ovid SP platform, from 1974 to 25 January 2021)
    - HTAD (searched via the University of York CRD platform, issue 4 of 4, October 2016)
    - NHS EED (searched via the University of York CRD platform, issue 2 of 4, April 2015)
    - International HTA Database (searched via the INAHTA website, January 25, 2021)

Grey Literature

- Searches of the following HTA body websites were conducted in January 2021 to identify any relevant HTAs:
    - All Wales Medicines Strategy Group (AWMSG; (www.awmsg.org/)
    - National Centre for Pharmacoeconomics (NCPE; http://www.ncpe.ie/)
    - National Institute for Health and Care Excellence (NICE; https://www.nice.org.uk/)
    - Scottish Medicines Consortium (SMC; https://www.scottishmedicines.org.uk/)

Economic Websites

- A supplementary search of the following sources was also conducted for any additional relevant studies:
    - The Cost-Effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center (https://cevr.tuftsmedicalcenter.org/databases/cea-registry)
    - The University of Sheffield Health Utilities Database (ScHARRHUD) (www.scharrhud.org/)
    - The EQ-5D Publications Database (www.euroqol.org/search-for-eq-5d-publications/)
    - Paediatric Economic Database Evaluation (PEDE database (http://pede.ccb.sickkids.ca/pede/search.jsp)

Conference Searches

A manual search of the following conference proceedings from the last three years (2018–2020) was performed:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
    - ISPOR 2018 (May 2018, Baltimore)
    - ISPOR Europe 2018 (November 2018, Barcelona)
    - ISPOR 2019 (May 2019, New Orleans)
    - ISPOR Europe 2019 (November 2019, Copenhagen)
    - ISPOR 2020 (May 2020, Virtual)
    - ISPOR Europe 2020 (November 2020, Virtual)
- Children's Tumor Foundation NF Conference
    - NF Conference 2019 (September 2019, San Francisco)
    - NF Conference 2020 (June 2020, Philadelphia)
- Joint Global Neurofibromatosis Conference (JGNC) 2018 (November 2018, Paris; this event combined the Children's Tumor Foundation NF Conference and European Neurofibromatosis Meeting in that year)
- European Society for Medical Oncology (ESMO) Congress
    - ESMO 2018 (October 2018, Munich)
    - ESMO 2019 (September–October 2019, Barcelona)

    - ESMO 2020 (September 2020, Virtual)
- American Society of Clinical Oncology (ASCO) Annual Meeting
    - ASCO 2018 (June 2018, Chicago)
    - ASCO 2019 (May–June 2019, Chicago)
    - ASCO 2020 (May–June 2020, Virtual)
- International Symposium on Pediatric Neuro-Oncology (ISPNO)
    - ISPNO 2018 (June–July 2018, Denver)
    - ISPNO 2020 (December 2020, Karuizawa)
- American Society of Pediatric Hematology/Oncology (ASPHO)
    - ASPHO 2018 (May 2018, Pittsburgh)
    - ASPHO 2019 (May 2019, New Orleans)
    - ASPHO 2020 (May 2020, Virtual)

Conference searches were limited to the past three years on the basis that any high-quality data published at conferences before this point, are likely to have been published in a journal article, so detected in the electronic database searches.

Bibliography Searches

The bibliographies of any relevant economic evaluations, HTAs, SLRs and (N)MAs were manually searched to identify any additional, relevant studies for inclusion.

Supplementary Searches

In addition to the database and grey literature searching performed, a manual search of materials provided by AstraZeneca was conducted. These materials included:

- A TLR conducted in 2019 on NF1 PN clinical studies
- A TLR conducted in 2020 to capture HRQoL instruments in NF1

17.4.2 The date on which the search was conducted.

Searches were conducted over the time-period presented in Table 60, between January and February 2021.

Table 60. Search dates for each SLR source

Resource searched	Date conducted
Electronic databases (MEDLINE, Embase, HTAD, NHS EED and the International HTA Database)	26th January 2021
HTA websites (AWMSG, NCPE, NICE, SMC)	22nd January 2021
Economic/health-state utility websites (CEA Registry, EQ-5D Publications Database, PEDE database, ScHARRHUD)	22nd January 2021
Conference proceedings (ASPHO, ASCO, Children's Tumor Foundation NF Conference, ESMO, ISPNO, ISPOR, JGNC)	5th February 2021
Manual bibliography searches of relevant SLRs/(N)MAs	8th February 2021
Supplementary searches (materials provided by AstraZeneca)	22nd January 2021

Abbreviations: ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; AWMSG: All Wales Medicines Strategy Group; CEA: Cost-Effectiveness Analysis; EQ-5D: EuroQol 5 Dimensions; ESMO: European Society for Medical Oncology; HTA: health technology assessment; HTAD: Health Technology Assessment Database; ISPNO: International Symposium on Pediatric Neuro-Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; JGNC: Joint Global Neurofibromatosis Conference; NCPE: National Centre for Pharmacoeconomics; NHS EED: NHS Economic Evaluation Database; NICE: National Institute for Health and Care Excellence; (N)MA: (network) meta-analysis; PEDE: Paediatric Economic Database Evaluation; ScHARRHUD: The University of Sheffield Health Utilities Database; SLR: systematic literature review; SMC: Scottish Medicines Consortium.

17.4.3 The date span of the search.

No date limit was applied to the electronic database, bibliography, or supplementary searches. All conference abstracts reviewed were limited to those published in the past three years (2018–2020). All HTAs included in the SLR were limited to those published in the past ten years (2011–2021).

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search terms used in MEDLINE and Embase are presented in Table 61 and Table 62 respectively. Search terms for the HTAD and NHS EED are presented in Table 64. Search terms for the International HTA Database are presented in Table 65.

Table 61. Search terms used in MEDLINE (searched via Ovid SP on 26th January 2021)

	#	Searches	Results
Disease area: NF1	1	exp Neurofibromatosis 1/	9,853
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kf.	7,977

	#	Searches	Results
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kf.	8,325
	4	or/1-3	16,491
Economic Evaluations	5	Cost-benefit analysis/	83,087
	6	"Costs and cost analysis"/	49,234
	7	Economics/	27,282
	8	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).ti,ab,kf.	156,366
	9	(economic evaluation$ or economic analysis or life year$ gained or ICER or QALY$ or DALY$ or quality adjusted or adjusted life year$ or disability adjusted life or qald$ or qale$ or qtime$).ti,ab,kf.	36,900
	10	Quality-adjusted life years/	12,812
	11	Value of life/	5,730
	12	or/5-11	280,816
Health-state Utilities and Health-related Quality of Life	13	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based).ti,ab,kf.	10,242
	14	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	815
	15	(multiattribute$ or multi attribute$).ti,ab.	940
	16	utility.ab. /freq=2	18,723
	17	(utilities or disutilit$).ti,ab,kf.	7,931
	18	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or euroqual or euroqol or euro qol or euroqual5d or euroqol5d or eq-sdq or eqsdq).ti,ab,kf.	12,226
	19	(short form$ or shortform$).ti,ab.	35,530
	20	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	23,035
	21	(sf6 or sf 6 or sf6d or sf 6d or sf six D or sfsixD or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf.	3,438
	22	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.	5,084
	23	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.	30
	24	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.	341
	25	(15D or 15-D or 15 dimension).ti,ab,kf.	5,438
	26	visual analog$ scale$.ti,ab,kf.	58,868
	27	(standard gamble$ or sg).ti,ab,kf.	11,415
	28	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	1979
	29	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kf.	83
	30	(hui or hui1 or hui2 or hui3 or rosser).ti,ab,kf.	1,711
	31	*quality of life/ and (quality of life or qol or hrqol).ti,ab,kf.	76,400
	32	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	28,976

	#	Searches	Results
	33	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).ti,ab,kf.	14,423
	34	quality of life/ and health-related quality of life.ti,ab,kf.	33,726
	35	quality of life/ and ec.fs.	10,371
	36	quality of life/ and (health adj3 status).ti,ab,kf.	9,377
	37	((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	40,495
	38	(brief pain inventory or BPI$ or patient health questionnaire$ or PHQ$ or (generalized anxiety disorder$ adj2 questionnaire) or GAD$ or PedsQL or Peds-QL or PROMIS or Patient-Reported Outcomes Measurement Information System or TACQOL or TNO AZL Childrens Quality of Life).ti,ab,kf.	64,719
	39	or/13-38	312,162
Healthcare Cost and Resource Use	40	Cost allocation/	2,008
	41	Cost control/	21,554
	42	Cost savings/	12,080
	43	Cost of illness/	28,121
	44	Cost sharing/	2,576
	45	"Deductibles and coinsurance"/	1,771
	46	Medical savings accounts/	538
	47	Health care costs/	40,631
	48	Direct service costs/	1198
	49	Drug costs/	16,376
	50	Employer health costs/	1,093
	51	Hospital costs/	11,326
	52	Health expenditures/	20,926
	53	Capital expenditures/	1,994
	54	exp economics, Hospital/	24,908
	55	exp economics, Medical/	14,237
	56	Economics, nursing/	4,002
	57	Economics, pharmaceutical/	2,969
	58	exp Budgets/	13,784
	59	Financial management/	16,632
	60	exp "Fees and charges"/	30,557
	61	(low adj cost).mp.	63,447
	62	(high adj cost).mp.	15,598
	63	(health?care adj cost$).mp.	12,665
	64	(fiscal or funding or financial or finance).ti,ab,kf.	158,485
	65	(cost adj estimate$).mp.	2,390
	66	(cost adj variable$).mp.	172

	#	Searches	Results
	67	(unit adj cost$).mp.	2,652
	68	(economic$ or pharmacoeconomic$ or price$ or pricing).ti,ab,kf.	343,211
	69	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).ti,ab,kf.	110,938
	70	((patient$ or caregiver$ or carer$ or social$ or society$ or family$ or work$) adj2 (burden$ or productiv$)).ti,ab,kf.	21,258
	71	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").ti,ab,kf.	291,563
	72	(absenteeism or presenteeism or employment or unemployment).ti,ab,kf. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	147,187
	73	or/40-72	1,129,706
Exclusion Terms	74	exp animals/ not exp humans/	4,780,075
	75	(comment or editorial).pt.	1,273,548
	76	historical article/	361,854
	77	or/74-76	6,344,185
Combined	78	4 and (12 or 39 or 73)	346
	79	78 not 77	332
	80	remove duplicates from 79	**327**

Databases: MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), from 1946 to January 25, 2021

Table 62. Search terms used in Embase (searched via Ovid SP on 26th January 2021)

	#	Searches	Results
Disease area: NF1	1	exp neurofibromatosis type 1/	3,605
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kw.	10,295
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kw.	12,188
	4	or/1-3	17,002
Economic Evaluations	5	Cost benefit analysis/ or exp economic evaluation/ or cost effectiveness analysis/ or cost minimization analysis/ or cost benefit/	314,489
	6	Economics/ or health economics/ or socioeconomics/ or economic aspect/ or pharmacoeconomics/	506,205
	7	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).ti,ab,kw.	216,756
	8	(economic evaluation$ or economic analysis or life year$ gained or ICER or QALY$ or DALY$ or quality adjusted or adjusted life year$ or disability adjusted life or qald$ or qale$ or qtime$).ti,ab,kw.	56,714

	#	Searches	Results
	9	Quality adjusted life year/	28,143
	10	or/5-9	859,893
Health-state Utilities and Health-related Quality of Life	11	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based).ti,ab,kw.	17,162
	12	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kw.	1,286
	13	(multiattribute$ or multi attribute$).ti,ab.	1,181
	14	utility.ab. /freq=2	29,072
	15	(utilities or disutilit$).ti,ab,kw.	13,025
	16	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or euroqual or euroqol or euro qol or euroqual5d or euroqol5d or eq-sdq or eqsdq).ti,ab,kw.	22,484
	17	(short form$ or shortform$).ti,ab.	48,392
	18	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	39,664
	19	(sf6 or sf 6 or sf6d or sf 6d or sf six D or sfsixD or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	4,726
	20	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kw.	8,656
	21	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kw.	57
	22	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kw.	347
	23	(15D or 15-D or 15 dimension).ti,ab,kw.	6,856
	24	visual analog$ scale$.ti,ab,kw.	83,767
	25	(standard gamble$ or sg).ti,ab,kw.	17,013
	26	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	2,923
	27	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kw.	160
	28	(hui or hui1 or hui2 or hui3 or rosser).ti,ab,kw.	2,572
	29	*quality of life/ and (quality of life or qol or hrqol).ti,ab,kw.	102,872
	30	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw.	80,202
	31	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).ti,ab,kw.	31,096
	32	quality of life/ and health-related quality of life.ti,ab,kw.	61,859
	33	quality of life/ and ec.fs.	44,809
	34	quality of life/ and (health adj3 status).ti,ab,kw.	17,012
	35	((qol or hrqol or quality of life).ti,kw. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	60,766
	36	(brief pain inventory or BPI$ or patient health questionnaire$ or PHQ$ or (generalized anxiety	99,078

	#	Searches	Results
		disorder$ adj2 questionnaire) or GAD$ or PedsQL or Peds-QL or PROMIS or Patient-Reported Outcomes Measurement Information System or TACQOL or TNO AZL Childrens Quality of Life).ti,ab,kw.	
	37	or/11-36	523,513
Healthcare Cost and Resource Use	38	Cost control/	69,766
	39	Cost of illness/	19,704
	40	Health care cost/	194,894
	41	Drug cost/	78,792
	42	Hospital cost/	22,162
	43	exp Budget/	30,070
	44	Financial management/	114,729
	45	health care financing/	13,435
	46	exp Fee/	40,691
	47	(low adj cost).mp.	71,635
	48	(high adj cost).mp.	20,458
	49	(health?care adj cost$).mp.	21,888
	50	(fiscal or funding or financial or finance).ti,ab,kw.	214,860
	51	(cost adj estimate$).mp.	3,580
	52	(cost adj variable$).mp.	280
	53	(unit adj cost$).mp.	4,702
	54	(economic$ or pharmacoeconomic$ or price$ or pricing).ti,ab,kw.	420,712
	55	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).ti,ab,kw.	154,951
	56	((patient$ or caregiver$ or carer$ or social$ or society$ or family$ or work$) adj2 (burden$ or productiv$)).ti,ab,kw.	35,568
	57	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").ti,ab,kw.	423,029
	58	(absenteeism or presenteeism or employment or unemployment).ti,ab,kw. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	153,338
	59	or/38-58	1,606,822
Exclusion Terms	60	("conference abstract" or "conference review").pt.	4,005,664
	61	limit 60 to yr="1974-2017"	3,038,161
	62	exp animals/ not exp humans/	4,750,859
	63	(comment or editorial).pt.	682,497
	64	historical article/	1
	65	or/61-64	8,180,843
Combined	66	4 and (10 or 37 or 59)	611

	#	Searches	Results
	67	66 not 65	464
	68	remove duplicates from 67	**454**

Database: Embase from 1974 to January 25, 2021

Table 63. Search terms used in the HTAD and NHS EED (searched via University of York CRD platform on 26th January 2021)

#	Searches	Results
1	(MeSH DESCRIPTOR Neurofibromatosis 1 EXPLODE ALL TREES)	2
2	(neurofibroma* adj2 ("1" or i or peripheral or von Recklinghausen))	6
3	(NF1 or NFI or NF-1 or NF-I)	5
4	(#1 or #2 or #3) in HTAD and NHS EED	6

Databases: HTAD, issue 4 of 4, October 2016; NHS EED, issue 2 of 4, April 2015

Table 64. Search terms used for the International HTA Database (searched via the INAHTA website on 26th January 2021)

#	Searches	Results
1	(Neurofibromatosis 1 [mh] or (((“neurofibroma* 1”) or (“neurofibroma* i”) or (“peripheral neurofibroma*”) or (“von Recklinghausen”))) or ((NF1 or NFI or NF-1 or NF-I))	7

Databases: INAHTA, searched on 26th January 2021.

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

HTA websites

The terms used for searching the HTA body websites are presented in Table 65.

Table 65. Search terms used for the HTA body websites (searched on 22nd January 2021)

HTA Body	Link	Search Strategy	Results	Included
AWSMG	http://www.awmsg.org/	The following terms were searched for[a]: 1. Plexiform neu 2. NF-1 3. NF1 4. Neurofibrom 5. Recklinghausen 6. Recklinghausen's	1	0
NCPE	http://www.ncpe.ie/		0	NA
NICE	https://www.nice.org.uk/		1	0
SMC	https://www.scottishmedicines.org.uk/Home		0	NA

[a]Results from NICE were filtered to give “Guidance” and “NICE Advice” only.

Abbreviations: AWMSG: All Wales Medicines Strategy Group; NA: not applicable; NCPE: National Centre for Pharmacoeconomics; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium

Economic websites

Search terms used for the online economic website searching are presented in Table 66.

Table 66. Search terms for the economic website searches (searched on 22nd January 2021)

Database	Link	Search Strategy	Results	Included
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	The CEA registry was searched for the following terms, with 'Methods' selected: 1. Plexiform neu 2. NF-1 3. NF1 4. Neurofibrom 5. Recklinghausen 6. Recklinghausen's This process was repeated, with 'Ratios' and 'Utility Weights' selected in turn.	28	0
EQ-5D Publications Database	https://euroqol.org/search-for-eq-5d-publications/	The following terms were searched for in turn: 1. Plexiform neu 2. NF-1 3. NF1 4. Neurofibrom 5. Recklinghausen 6. Recklinghausen's	37	0
PEDE Database	http://pede.ccb.sickkids.ca/pede/search.jsp		3	0
ScHARR HUD	https://www.scharrhud.org/index.php?recordsN1&m=search	The following terms were searched for in turn, with abstract [AB] specified in the 'Field' drop-down menu: 1. Plexiform neu 2. NF-1 3. NF1 4. Neurofibrom 5. Recklinghausen 6. Recklinghausen's	1	0

Abbreviations: CEA: Cost-Effectiveness Analysis; EQ-5D: EuroQol 5 Dimensions; NF1: type 1 neurofibromatosis; PEDE: Paediatric Economic Database Evaluation; ScHARRHUD: The University of Sheffield Health Utilities Database

Conference Searches

Abstract books (where available) or the relevant conference website were searched for eight selected conferences for the past three years, in order to identify any additional studies eligible for inclusion in the SLR. The total results and number of included records for each conference are presented in Table 67.

Table 67. Search strategies for congress searching (performed 5th February 2021)

Conference	Link	Search Strategy	Number screened	Number included		
				EEs	HRQoL	CRU
ASCO Annual Meeting: 2018	https://meetinglibrary.asco.org/	The following string was searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:”von Recklinghausen”)	40	0	0	0
ASCO Annual Meeting: 2019	https://meetinglibrary.asco.org/	The following string was searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:”von Recklinghausen”)	57	0	0	0
ASCO Annual Meeting: 2020	https://meetinglibrary.asco.org/	The following string was searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:”von Recklinghausen”)	47	0	0	0
ASPHO 2018	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM18&ssoOverride=OFF&USERPID=PUBLIC	The 2018 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. “NF-1” 3. NF1 4. Plexiform 5. Von Recklinghausen's	2	0	0	0

Conference	Link	Search Strategy	Number screened	Number included		
				EEs	HRQoL	CRU
ASPHO 2019	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM19&ssoOverride=OFF&USERPID=PUBLIC	The 2019 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. "NF-1" 3. NF1 4. Plexiform 5. Von Recklinghausen's	3	0	0	0
ASPHO 2020	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM20&ssoOverride=OFF&USERPID=PUBLIC	The 2020 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. "NF-1" 3. NF1 4. Plexiform 5. Von Recklinghausen's	4	0	0	0
Children's Tumor Foundation NF Conference: 2019[a]	https://www.ctf.org/get-involved/nf-conference	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: 1. Type 1 2. NF-1 3. NF1 4. Von Recklinghausen's	145	0	0	0
Children's Tumor Foundation NF Conference: 2020[a]	https://www.ctf.org/get-involved/nf-conference	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: 1. Type 1 2. NF-1 3. NF1 4. Von Recklinghausen's	59	0	0	0

Conference	Link	Search Strategy	Number screened	Number included		
				EEs	HRQoL	CRU
ESMO Congress 2018	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress	The 2018 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. “NF-1” 3. NF1 4. Plexiform 5. Von Recklinghausen's	6	0	0	0
ESMO Congress 2019	https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress	The 2019 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. “NF-1” 3. NF1 4. Plexiform 5. Von Recklinghausen's	14	0	0	0
ESMO Congress 2020	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020	The 2020 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. “NF-1” 3. NF1 4. Plexiform 5. Von Recklinghausen's	5	0	0	0
ISPNO: 2018[b]	http://ispno2018.com/	The abstract book in PDF format was searched using the ‘Ctrl + F’ function, to search the following terms one by one: 1. Type 1 2. NF-1 3. NF1 4. Von Recklinghausen's	377	0	0	0

Conference	Link	Search Strategy	Number screened	Number included		
				EEs	HRQoL	CRU
ISPNO: 2020[b]	http://ispno2020.umin.jp/	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: 1. Type 1 2. NF-1 3. NF1 4. Von Recklinghausen's	49	0	0	0
ISPOR Annual European Meeting 2018	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2018-11, ISPOR Europe 2018, Barcelona, Spain" under the dropdown 'Conference' menu: 1. Plexiform neu* 2. NF-1 3. NF1 4. Neurofibrom* 5. Von Recklinghausen's	0	0	0	0
ISPOR Annual European Meeting 2019	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2019-11, ISPOR Europe 2019, Copenhagen, Denmark" under the dropdown 'Conference' menu: 1. 1. Plexiform neu* 2. 2. NF-1 3. 3. NF1 4. 4. Neurofibrom* 5. 5. Von Recklinghausen's	0	0	0	0
ISPOR Annual European Meeting 2020	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2020-11, ISPOR	5	0	0	0

Conference	Link	Search Strategy	Number screened	Number included		
				EEs	HRQoL	CRU
		Europe 2020, Milan, Italy" under the dropdown 'Conference' menu: 1. Plexiform neu* 2. NF-1 3. NF1 4. Neurofibrom* 5. Von Recklinghausen's				
ISPOR Annual International Meeting 2018	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2018-05, ISPOR 2018, Baltimore, MD, USA" under the dropdown 'Conference' menu: 1. Plexiform neu* 2. NF-1 3. NF1 4. Neurofibrom* 5. Von Recklinghausen's	0	0	0	0
ISPOR Annual International Meeting 2019	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2019-05, ISPOR 2019, New Orleans, LA, USA" under the dropdown 'Conference' menu: 1. Plexiform neu* 2. NF-1 3. NF1 4. Neurofibrom* 5. Von Recklinghausen's	0	0	0	0
ISPOR Annual International Meeting 2020	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2020-05, ISPOR 2020,	0	0	0	0

Conference	Link	Search Strategy	Number screened	Number included		
				EEs	HRQoL	CRU
		Orlando, FL, USA" under the dropdown 'Conference' menu: 1 Plexiform neu* 2 NF-1 3 NF1 4 Neurofibrom* 5 Von Recklinghausen's				
JGNC 2018[a]	http://www.nf-paris2018.com/EventPortal/Information/NF2018/WELCOME.aspx	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: 1. Type 1 2. NF-1 3. NF1 4. Von Recklinghausen's	291	0	2	1

Footnotes: [a]In 2018, the Children's Tumor Foundation NF Conference was combined with the European Neurofibromatosis Meeting and ran as JGNC 2018; [b]held biannually
Abbreviations: ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; CRU: cost and resource use; EE: economic evaluation; ESMO: European Society for Medical Oncology; HRQoL: health-related quality of life; ISPNO: International Symposium on Pediatric Neuro-Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; JGNC: Joint Global Neurofibromatosis Conference; NF1: type 1 neurofibromatosis

17.4.6 The inclusion and exclusion criteria

Eligibility criteria for the inclusion and exclusion of studies are presented in Table D in Section 11.1.2.

Each record identified in the SLR searches were assessed for eligibility across all three data streams (cost-effectiveness, HRQoL, and cost and resource use simultaneously). Each study identified could therefore be included in one or more of the three data streams.

17.4.7 The data abstraction strategy

The most stringent record screening process as recommended by the Cochrane Collaboration was followed.[175] The title and abstract of each record were reviewed against the eligibility criteria presented in Table D in Section 11.1.2. by two independent reviewers. Where the applicability of the inclusion criteria was unclear, articles were included at this stage to ensure that all potentially relevant studies were captured. The two independent reviewers then compared their results, and any disagreements were resolved by discussion until a consensus was met, with a third independent reviewer asked to arbitrate when necessary.

For studies meeting the eligibility criteria after title and abstract review, the full text was reviewed against the eligibility criteria by two independent reviewers. Articles with insufficient information to ensure they met the eligibility criteria were excluded at this stage, to ensure that only relevant articles were ultimately included in the SLR. Again, two independent reviewers compared results, and any conflicts were resolved by discussion or the arbitration of a third independent reviewer.

Key information from studies meeting the eligibility criteria after full-text review were extracted by a single reviewer into a pre-specified data extraction grid in Microsoft Word. Any data extracted were verified for accuracy by a second, independent reviewer.

17.4.8 Included and excluded study tables

A list of studies included in the HRQoL stream of the SLR can be found in Table 68. A list of studies excluded in the economic evaluations and HRQoL streams following full-text review can be found in Table 69, and Table 70 respectively, alongside reasoning for exclusion.

Table 68. List of studies included in the HRQoL SLR

#	Study name	Citation
26	SPRINT	Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. New England Journal of Medicine 2020;382:1430-1442.
27		Wolters P. Prospective Patient-Reported Outcomes (PROs) Document Clinical Benefit in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PNs) on

#	Study name	Citation
		SPRINT: a Phase II Trial of the MEK 1/2 Inhibitor Selumetinib. Joint Global Neurofibromatosis Conference 2018.
28	Hamoy-Jimenez 2020	Hamoy-Jimenez G, Kim R, Suppiah S, et al. Quality of life in patients with neurofibromatosis type 1 and 2 in Canada. Neuro-oncology Advances 2020;2:i141-i149.
29	Lai 2019	Lai JS, Jensen SE, Charrow J, et al. Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders Measurement System to Evaluate Quality of Life for Children and Adolescents with Neurofibromatosis Type 1 Associated Plexiform Neurofibroma. Journal of Pediatrics 2019;206:190-196.
30	Ren 2020	Ren JY, Gu YH, Wei CJ, et al. Evaluation and Factors of Quality of Life Among Patients With Neurofibromatosis Type 1-Associated Craniofacial Plexiform Neurofibromas. The Journal of craniofacial surgery 2020;31:347-350.
31	Rosser 2018	Rosser T. Substantial Pain and Reduced Quality of Life (QOL) in Adolescents and Young Adults (AYA) with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibromas (PNs) Enrolled in NF Consortium PN Clinical Trials. International Symposium on Pediatric Neuro-Oncology (ISPNO) 2018.
32	Weiss 2014 (NCT00634270)	Weiss B, Widemann BC, Wolters P, et al. Sirolimus for non-progressive NF1-associated plexiform neurofibromas: An NF clinical trials consortium phase II study. Pediatric Blood and Cancer 2014;61:982-986.
33	Widemann 2014 (NCT00021541)	Widemann BC, Dombi E, Gillespie A, et al. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro-Oncology 2014;16:707-718.
34	Wolkenstein 2009	Wolkenstein P, Rodriguez D, Ferkal S, et al. Impact of neurofibromatosis 1 upon quality of life in childhood: A cross-sectional study of 79 cases. British Journal of Dermatology 2009;160:844-848.
35	Wolters 2015	Wolters PL, Burns KM, Martin S, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. American Journal of Medical Genetics, Part A 2015;167:2103-2113.

Abbreviations: HRQoL: health related quality of life; SLR: systematic literature review

Table 69. List of studies excluded in the economic evaluations SLR at full-text review and reasoning for exclusion

#	Citation	Reason for exclusion
6	Acarturk TO, Yigenoglu B, Pekedis O. Excision and "transcutaneous" lift in patients with neurofibromatosis of the fronto-temporo-orbital and auricular regions. Journal of Craniofacial Surgery 2009;20:771-4.	Irrelevant study design
7	Afridi SK, Leschziner GD, Ferner RE. Prevalence and clinical presentation of headache in a National Neurofibromatosis 1	Doesn't report a relevant economic evaluation

#	Citation	Reason for exclusion
	Service and impact on quality of life. American Journal of Medical Genetics, Part A 2015;167:2282-2285.	
8	Algermissen B, Muller U, Katalinic D, et al. CO<inf>2</inf> laser treatment of neurofibromas of patients with neurofibromatosis type 1: Five years experience. Medical Laser Application 2001;16:265-274.	Doesn't report a relevant economic evaluation
9	Avery RA, Hardy KK. Vision specific quality of life in children with optic pathway gliomas. Journal of Neuro-Oncology 2014;116:341-347.	Doesn't report a relevant economic evaluation
10	Bergqvist C, Servy A, Valeyrie-Allanore L, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet journal of rare diseases 2020;15:37.	Irrelevant study design
11	Bicudo NP, de Menezes Neto BF, da Silva de Avo LR, et al. Quality of Life in Adults with Neurofibromatosis 1 in Brazil. Journal of genetic counseling 2016;25:1063-1074.	Doesn't report a relevant economic evaluation
12	Bottesi G, Spoto A, Trevisson E, et al. Dysfunctional coping is related to impaired skin-related quality of life and psychological distress in patients with neurofibromatosis type 1 with major skin involvement. British Journal of Dermatology 2020;182:1449-1457.	Doesn't report a relevant economic evaluation
13	Brenaut E, Nizery-Guermeur C, Audebert-Bellanger S, et al. Clinical Characteristics of Pruritus in Neurofibromatosis 1. Acta Dermato-Venereologica 2016;96:398-9.	Doesn't report a relevant economic evaluation
14	Brunt LM, Lairmore TC, Doherty GM, et al. Adrenalectomy for familial pheochromocytoma in the laparoscopic era. Annals of Surgery 2002;235:713-721.	Irrelevant study design
15	Chamseddin BH, Hernandez L, Solorzano D, et al. Robust surgical approach for cutaneous neurofibroma in neurofibromatosis type 1. JCI Insight 2019;4 (11) (no pagination).	Doesn't report a relevant economic evaluation
16	Cipolletta S, Spina G, Spoto A. Psychosocial functioning, self-image, and quality of life in children and adolescents with neurofibromatosis type 1. Child: care, health and development 2018;44:260-268.	Doesn't report a relevant economic evaluation
17	Cohen JS, Levy HP, Sloan J, et al. Depression among adults with neurofibromatosis type 1: Prevalence and impact on quality of life. Clinical Genetics 2015;88:425-430.	Doesn't report a relevant economic evaluation
18	Copley-Merriman C, Yang X, Juniper M, et al. Pro85 Impact of Neurofibromatosis Type 1 and Plexiform Neurofibromas on Patient-Reported Health-Related Quality of Life. Value in Health 2020;23 (Supplement 1):S344.	Irrelevant study design
19	Cosyns M, Mortier G, Janssens S, et al. Voice-related quality of life in adults with neurofibromatosis type 1. Journal of Voice 2012;26:e57-e62.	Doesn't report a relevant economic evaluation
20	Coutinho V, Camara-Costa H, Kemlin I, et al. The Discrepancy between Performance-Based Measures and Questionnaires when Assessing Clinical Outcomes and Quality of Life in Pediatric Patients with Neurological Disorders. Applied neuropsychology 2017;Child. 6:255-261.	Doesn't report a relevant economic evaluation

#	Citation	Reason for exclusion
21	Dakwar E, Smith WD, Malone KT, et al. Minimally invasive lateral extracavitary resection of foraminal neurofibromas. Journal of Clinical Neuroscience 2011;18:1510-2.	Doesn't report a relevant economic evaluation
22	Dolan KD, Yuh WT. Gadolinium-enhanced facial nerves: accompanying bilateral acoustic tumors in patient with neurofibromatosis. Annals of Otology, Rhinology & Laryngology 1989;98:747-8.	Irrelevant study design
23	Doser K, Andersen EW, Kenborg L, et al. Clinical characteristics and quality of life, depression, and anxiety in adults with neurofibromatosis type 1: A nationwide study. American Journal of Medical Genetics, Part A 2020;182:1704-1715.	Doesn't report a relevant economic evaluation
24	Draucker CB, Nutakki K, Varni JW, et al. The health-related quality of life of children, adolescents, and young adults with neurofibromatosis type 1 and their families: Analysis of narratives. Journal for specialists in pediatric nursing : JSPN 2017;22.	Doesn't report a relevant economic evaluation
25	Ehara Y, Koga M, Imafuku S, et al. Distribution of diffuse plexiform neurofibroma on the body surface in patients with neurofibromatosis 1. Journal of Dermatology 2020;47:190-192.	Doesn't report a relevant economic evaluation
26	Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. The Lancet Oncology 2019;20:1011-1022.	Doesn't report a relevant economic evaluation
27	Farmer JP, Khan S, Khan A, et al. Neurofibromatosis type 1 and the pediatric neurosurgeon: A 20-year institutional review. Pediatric Neurosurgery 2002;37:122-136.	Doesn't report a relevant economic evaluation
28	Ferner RE, Thomas M, Mercer G, et al. Evaluation of quality of life in adults with neurofibromatosis 1 (NF1) using the Impact of NF1 on Quality Of Life (INF1-QOL) questionnaire. Health and Quality of Life Outcomes 2017;15 (1) (no pagination).	Doesn't report a relevant economic evaluation
29	Fisher MJ, Shih CS, Rhodes SD, et al. Cabozantinib for neurofibromatosis type 1-related plexiform neurofibromas: a phase 2 trial. Nat Med 2021;27:165-173.	Doesn't report a relevant economic evaluation
30	Fjermestad KW, Nyhus L, Kanavin OJ, et al. Health Survey of Adults with Neurofibromatosis 1 Compared to Population Study Controls. Journal of genetic counseling 2018;27:1102-1110.	Doesn't report a relevant economic evaluation
31	Fjermestad KW. Health complaints and work experiences among adults with neurofibromatosis 1. Occupational medicine (Oxford, England) 2019;69:504-510.	Doesn't report a relevant economic evaluation
32	Fletcher AN, Schwend RM. The Ecuador Pediatric Spine Deformity Surgery Program: An SRS-GOP Site, 2008-2016. Spine Deformity 2019;7:220-227.	Irrelevant study design
33	Flood TF, Stence NV, Maloney JA, et al. Pediatric brain: Repeated exposure to linear gadolinium-based contrast material is associated with increased signal intensity at unenhanced T1-weighted MR imaging. Radiology 2017;282:222-228.	Irrelevant population

#	Citation	Reason for exclusion
34	Freedman I, Koo A, Yeagle E, et al. Does neurofibromatosis 1 status impact outcomes for pediatric/young adults undergoing spinal fusion? Surgical Neurology International 2020;11 (60) (no pagination).	Doesn't report a relevant economic evaluation
35	Furlong W, Barr RD, Feeny D, et al. Patient-focused measures of functional health status and health-related quality of life in pediatric orthopedics: A case study in measurement selection. Health and Quality of Life Outcomes 2005;3 (no pagination).	Irrelevant study design
36	Gilboa Y, Rosenblum S, Fattal-Valevski A, et al. Application of the International Classification of Functioning, Disability and Health in children with neurofibromatosis type 1: a review. Developmental Medicine & Child Neurology 2010;52:612-9.	Irrelevant study design
37	Giudice G, Favia G, Tempesta A, et al. Confocal microscopy predicts the risk of recurrence and malignant transformation of mucocutaneous neurofibromas in NF-1: An observational study. Dermatology Research and Practice 2018;2018 (no pagination).	Doesn't report a relevant economic evaluation
38	Goetsch Weisman A, Haws T, Lee J, et al. Transition Readiness Assessment in Adolescents and Young Adults with Neurofibromatosis Type 1 (NF1). Comprehensive child and adolescent nursing 2020:1-17.	Doesn't report a relevant economic evaluation
39	Graf A, Landolt MA, Mori AC, et al. Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1. Journal of Pediatrics 2006;149:348-353.	Doesn't report a relevant economic evaluation
40	Griffiths S, Thompson P, Frayling I, et al. Molecular diagnosis of neurofibromatosis type 1: 2 Years experience. Familial Cancer 2007;6:21-34.	Doesn't report a relevant economic evaluation
41	Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. New England Journal of Medicine 2020;382:1430-1442.	Doesn't report a relevant economic evaluation
42	Guiraud M, Bouroubi A, Beauchamp R, et al. Cutaneous neurofibromas: Patients' medical burden, current management and therapeutic expectations: Results from an online European patient community survey. Orphanet Journal of Rare Diseases 2019;14 (1) (no pagination).	Doesn't report a relevant economic evaluation
43	Hamoy-Jimenez G, Kim R, Suppiah S, et al. Quality of life in patients with neurofibromatosis type 1 and 2 in Canada. Neuro-oncology Advances 2020;2:i141-i149.	Doesn't report a relevant economic evaluation
44	Hivelin M, Wolkenstein P, Lepage C, et al. Facial aesthetic unit remodeling procedure for neurofibromatosis type 1 hemifacial hypertrophy: report on 33 consecutive adult patients. Plastic & Reconstructive Surgery 2010;125:1197-207.	Doesn't report a relevant economic evaluation
45	Holzapfel J, Kandels D, Schmidt R, et al. Favorable prognosis in pediatric brainstem low-grade glioma: Report from the German SIOP-LGG 2004 cohort. International Journal of Cancer 2020;146:3385-3396.	Doesn't report a relevant economic evaluation
46	Iannicelli E, Rossi G, Almberger M, et al. Integrated imaging in peripheral nerve lesions in type 1 neurofibromatosis. La Radiologia medica 2002;103:332-343.	Doesn't report a relevant economic evaluation

#	Citation	Reason for exclusion
47	Imperato A CG, Meccariello G. Optic pathway gliomas of the pediatric age: impact of neurosurgery on quality of life. Child's Nervous System 2018;34:1022.	Doesn't report a relevant economic evaluation
48	Kalakoti P, Missios S, Menger R, et al. Association of risk factors with unfavorable outcomes after resection of adult benign intradural spine tumors and the effect of hospital volume on outcomes: an analysis of 18, 297 patients across 774 US hospitals using the National Inpatient Sample (2002-2011). Neurosurgical focus 2015;39:E4.	Doesn't report a relevant economic evaluation
49	Kodra Y, Giustini S, Divona L, et al. Health-related quality of life in patients with neurofibromatosis type 1: A survey of 129 Italian patients. Dermatology 2009;218:215-220.	Doesn't report a relevant economic evaluation
50	Kondyli M, Larouche V, Saint-Martin C, et al. Trametinib for progressive pediatric low-grade gliomas. Journal of Neuro-Oncology 2018;140:435-444.	Irrelevant study design
51	Kongkriangkai AM, King C, Martin LJ, et al. Substantial pain burden in frequency, intensity, interference and chronicity among children and adults with neurofibromatosis Type 1. American Journal of Medical Genetics, Part A 2019;179:602-607.	Doesn't report a relevant economic evaluation
52	Krab LC, Oostenbrink R, de Goede-Bolder A, et al. Health-Related Quality of Life in Children with Neurofibromatosis Type 1: Contribution of Demographic Factors, Disease-Related Factors, and Behavior. Journal of Pediatrics 2009;154:420-425.Irrelevant study design.	Doesn't report a relevant economic evaluation
53	Kurucan E, Bernstein DN, Thirukumaran C, et al. National Trends in Spinal Fusion Surgery for Neurofibromatosis. Spine Deformity 2018;6:712-718.	Doesn't report a relevant economic evaluation
54	Kuwahara M, Yurugi S, Iioka H, et al. Problems on resecting the neurofibromatosis type 1 from experiences of 17 patients. [Japanese]. Skin Research 2004;3:591-596.	Doesn't report a relevant economic evaluation
55	Lai JS, Jensen SE, Charrow J, et al. Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders Measurement System to Evaluate Quality of Life for Children and Adolescents with Neurofibromatosis Type 1 Associated Plexiform Neurofibroma. Journal of Pediatrics 2019;206:190-196.	Doesn't report a relevant economic evaluation
56	Lantieri L, Grimbert P, Ortonne N, et al. Face transplant: long-term follow-up and results of a prospective open study. The Lancet 2016;388:1398-1407.	Irrelevant study design
57	Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II weekly vinblastine for chemotherapy-naive children with progressive low-grade glioma: A Canadian pediatric brain tumor consortium study. Journal of Clinical Oncology 2016;34:3537-3543.	Doesn't report a relevant economic evaluation
58	Lundar T, Due-Tonnessen BJ, Egge A, et al. Neurosurgical treatment of pediatric low-grade midbrain tumors: a single consecutive institutional series of 15 patients. Journal of neurosurgery 2014;Pediatrics. 14:598-603.	Irrelevant study design

#	Citation	Reason for exclusion
59	Lyu Q, Zhou C, Song Y, et al. Does spinal deformity correction of non-dystrophic scoliosis in neurofibromatosis type I with one-stage posterior pedicle screw technique produce outcomes similar to adolescent idiopathic scoliosis? Spine Journal 2017;17:1850-1858.	Doesn't report a relevant economic evaluation
60	Maloney E, Stanescu AL, Perez FA, et al. Surveillance magnetic resonance imaging for isolated optic pathway gliomas: is gadolinium necessary? Pediatric Radiology 2018;48:1472-1484.	Doesn't report a relevant economic evaluation
61	Marsault P, Ducassou S, Menut F, et al. Diagnostic performance of an unenhanced MRI exam for tumor follow-up of the optic pathway gliomas in children. Neuroradiology 2019;61:711-720.	Doesn't report a relevant economic evaluation
62	Marsault P, Menut F, Bessou P, et al. Optic pathway gliomas: MRI follow-up including imaging with gadolinium-based contrast agent: Accuracy of non-enhancement sequences for diagnosis of progression. Pediatric Radiology 2019;49 (Supplement 2):S311.	Doesn't report a relevant economic evaluation
63	Mauger D, Zeller J, Revuz J, et al. Psychological impact of neurofibromatosis type 1: Analysis of interviews with 12 patients to evaluate quality of life. [French]. Annales de Dermatologie et de Venereologie 1999;126:619-620.	Irrelevant study design
64	Merker VL, Bredella MA, Cai W, et al. Relationship between whole-body tumor burden, clinical phenotype, and quality of life in patients with neurofibromatosis. American Journal of Medical Genetics, Part A 2014;164:1431-1437.	Doesn't report a relevant economic evaluation
65	Metalwala Z, Okunseri C, Fletcher S, et al. Orthognathic Surgical Outcomes in Patients With and Without Craniofacial Anomalies. Journal of Oral and Maxillofacial Surgery 2018;76:436.Irrelevant study design-436.e8.	Irrelevant population
66	Miraglia E, Calvieri S, Giustini S. Pruritus in neurofibromatosis type 1. Giornale Italiano di Dermatologia e Venereologia 2018;153:120-122.	Doesn't report a relevant economic evaluation
67	Morandell E, Salandin M, Mantovan F. [Experiences of patients with neurofibromatosis type 1 and their families or caregivers]. Kinderkrankenschwester 2013;32:102-5.	Irrelevant study design
68	Muram TM, Stevenson DA, Watts-Justice S, et al. A cost savings approach to SPRED1 mutational analysis in individuals at risk for neurofibromatosis type 1. American Journal of Medical Genetics, Part A 2013;161:467-472.	Doesn't report a relevant economic evaluation
69	Newman WC, Berry-Candelario J, Villavieja J, et al. Improvement in Quality of Life Following Surgical Resection of Benign Intradural Extramedullary Tumors: A Prospective Evaluation of Patient-Reported Outcomes. Neurosurgery 2021.	Irrelevant population
70	Nutakki K, Hingtgen CM, Monahan P, et al. Development of the adult PedsQL TM neurofibromatosis type 1 module: initial feasibility, reliability and validity. Health & Quality of Life Outcomes 2013;11:21.	Doesn't report a relevant economic evaluation

#	Citation	Reason for exclusion
71	Nutakki K, Hingtgen CM, Monahan P, et al. Development of the Adult PedsQLTM Neurofibromatosis Type 1 Module: Initial Feasibility, Reliability and Validity. Health and Quality of Life Outcomes 2013;11 (1) (no pagination).	Doesn't report a relevant economic evaluation
72	Nutakki K, Varni JW, Steinbrenner S, et al. Development of the pediatric quality of life inventory neurofibromatosis type 1 module items for children, adolescents and young adults: qualitative methods. Journal of Neuro-Oncology 2017;132:135-143.	Doesn't report a relevant economic evaluation
73	Nutakki K, Varni JW, Swigonski NL. PedsQL Neurofibromatosis Type 1 Module for children, adolescents and young adults: feasibility, reliability, and validity. Journal of Neuro-Oncology 2018;137:337-347.	Doesn't report a relevant economic evaluation
74	Oostenbrink R, Spong K, de Goede-Bolder A, et al. Parental Reports of Health-Related Quality Of Life in Young Children with Neurofibromatosis Type 1: Influence of Condition Specific Determinants. Journal of Pediatrics 2007;151:182-186.Irrelevant population.	Doesn't report a relevant economic evaluation
75	Pacheco-Cuellar G, Castaneda-Saldana I, Valdez-Andrade J, et al. P-294 Incorporating genetic counseling service into the gastrointestinal tumor board: Experience, obstacles, and opportunities in a Mexican center. Annals of Oncology 2020;31 (Supplement 3):S185-S186.	Irrelevant study design
76	Page PZ, Page GP, Ecosse E, et al. Impact of neurofibromatosis 1 on quality of life: A cross-sectional study of 176 American cases. American Journal of Medical Genetics, Part A 2006;140:1893-1898.	Doesn't report a relevant economic evaluation
77	Payne JM, Barton B, Ullrich NJ, et al. Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1. Neurology 2016;87:2575-2584.	Doesn't report a relevant economic evaluation
78	Reichman M, Riklin E, Macklin E, et al. Virtual mind-body treatment for adolescents with neurofibromatosis: Study protocol for a single-blind randomized controlled trial. Contemporary Clinical Trials 2020;95 (no pagination).	Doesn't report a relevant economic evaluation
79	Ren JY, Gu YH, Wei CJ, et al. Evaluation and Factors of Quality of Life Among Patients With Neurofibromatosis Type 1-Associated Craniofacial Plexiform Neurofibromas. The Journal of craniofacial surgery 2020;31:347-350.	Irrelevant population
80	Ruegg EM, Hivelin M, Hemery F, et al. Face transplantation program in France: a cost analysis of five patients. Transplantation 2012;93:1166-72.	Doesn't report a relevant economic evaluation
81	Saltik S, Basgul SS. [Quality of life in children with neurofibromatosis type 1, based on their mothers' reports]. Turk Psikiyatri Dergisi 2013;24:25-34.	Irrelevant study design
82	Sanagoo A, Jouybari L, Koohi F, et al. Evaluation of QoL in neurofibromatosis patients: a systematic review and meta-analysis study. BMC Neurology 2019;19:123.	Doesn't report a relevant economic evaluation
83	Schooler GR, Davis JT, Daldrup-Link HE, et al. Current utilization and procedural practices in pediatric whole-body MRI. Pediatric Radiology 2018;48:1101-1107.	Irrelevant study design

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84	Shah M, Mavers M, Bree A, et al. Quality of life and depression assessment in nevoid basal cell carcinoma syndrome. International Journal of Dermatology 2011;50:268-76.	Doesn't report a relevant economic evaluation
85	Shin DW, Sohn MJ, Kim HS, et al. Clinical analysis of spinal stereotactic radiosurgery in the treatment of neurogenic tumors. Journal of neurosurgery 2015;Spine. 23:429-437.	Irrelevant population
86	Soghi I, Saeedi S, Sanagoo A, et al. Quality of life in a group of Iranian patients with neurofibromatosis type 1 with cutaneous expressions. [Persian]. Journal of Mazandaran University of Medical Sciences 2018;28:95-103.	Irrelevant population
87	Soulier G, van Leeuwen BM, Putter H, et al. Quality of Life in 807 Patients with Vestibular Schwannoma: Comparing Treatment Modalities. Otolaryngology - Head and Neck Surgery (United States) 2017;157:92-98.	Doesn't report a relevant economic evaluation
88	Spuijbroek AT, Oostenbrink R, Landgraf JM, et al. Health-related quality of life in preschool children in five health conditions. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:779-786.	Irrelevant population
89	Tora MS, Xenos D, Texakalidis P, et al. Treatment of neurofibromatosis 1-associated malignant peripheral nerve sheath tumors: a systematic review. Neurosurgical Review 2020;43:1039-1046.	Doesn't report a relevant economic evaluation
90	Tsang E, Birch P, Friedman JM. Valuing gene testing in children with possible neurofibromatosis 1. Clinical Genetics 2012;82:591-593.	Irrelevant study design
91	Turkson L, Mamuszka H, Grimshaw K, et al. Abstract 5288: MPNST treatment and diagnosis in NF1: A health economic model. Cancer Research 2018;78:5288.	Doesn't report a relevant economic evaluation
92	Van Der Vaart T, Rietman AB, Plasschaert E, et al. Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology 2016;86:154-160.	Doesn't report a relevant economic evaluation
93	Vardarinos A, Zafeiriou DI, Vargiami E, et al. Parental reports of health-related quality of life in greek children with neurofibromatosis type 1. Journal of Pediatrics 2009;155:453.	Doesn't report a relevant economic evaluation
94	Varni JW, Nutakki K, Swigonski NL. Cognitive functioning and pain interference mediate pain predictive effects on health-related quality of life in pediatric patients with Neurofibromatosis Type 1. European Journal of Paediatric Neurology. 2020.	Doesn't report a relevant economic evaluation
95	Varni JW, Nutakki K, Swigonski NL. Pain, skin sensations symptoms, and cognitive functioning predictors of health-related quality of life in pediatric patients with Neurofibromatosis Type 1. Quality of Life Research 2019;28:1047-1052.	Doesn't report a relevant economic evaluation
96	Varni JW, Nutakki K, Swigonski NL. Speech difficulties and patient health communication mediating effects on worry and health-related quality of life in children, adolescents, and young adults with Neurofibromatosis Type 1. American Journal of Medical Genetics, Part A 2019;179:1476-1482.	Doesn't report a relevant economic evaluation

#	Citation	Reason for exclusion
97	Vassallo G, Mughal Z, Robinson L, et al. Perceived fatigue in children and young adults with neurofibromatosis type 1. Journal of Paediatrics & Child Health 2020;56:878-883.	Doesn't report a relevant economic evaluation
98	Vranceanu AM, Merker VL, Park E, et al. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: A systematic review of the literature. Journal of Neuro-Oncology 2013;114:257-262.	Doesn't report a relevant economic evaluation
99	Vranceanu AM, Merker VL, Park ER, et al. Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature. Journal of Neuro-Oncology 2015;122:219-28.	Irrelevant study design
100	Wang J, Liu C, Wang C, et al. Early and Midterm Outcomes of Surgical Correction for Severe Dystrophic Cervical Kyphosis in Patients with Neurofibromatosis Type 1: A Retrospective Multicenter Study. World Neurosurgery 2019;127:Irrelevant study design190-Irrelevant study design200.	Irrelevant study design
101	Weiss B, Widemann BC, Wolters P, et al. Sirolimus for non-progressive NF1-associated plexiform neurofibromas: An NF clinical trials consortium phase II study. Pediatric Blood and Cancer 2014;61:982-986.	Doesn't report a relevant economic evaluation
102	Widemann BC, Dombi E, Gillespie A, et al. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro-Oncology 2014;16:707-718.	Doesn't report a relevant economic evaluation
103	Wiener L, Battles H, Bedoya SZ, et al. Identifying Symptoms of Distress in Youth Living with Neurofibromatosis Type 1 (NF1). Journal of Genetic Counseling 2018;27:115-123.	Doesn't report a relevant economic evaluation
104	Wolkenstein P, Durand-Zaleski I, Moreno JC, et al. Cost evaluation of the medical management of neurofibromatosis 1: A prospective study on 201 patients. British Journal of Dermatology 2000;142:1166-1170.	Doesn't report a relevant economic evaluation
105	Wolkenstein P, Loundou A, Barrau K, et al. Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. Journal of the American Academy of Dermatology 2007;56:621-3.	Doesn't report a relevant economic evaluation
106	Wolkenstein P, Rodriguez D, Ferkal S, et al. Impact of neurofibromatosis 1 upon quality of life in childhood: A cross-sectional study of 79 cases. British Journal of Dermatology 2009;160:844-848.	Doesn't report a relevant economic evaluation
107	Wolkenstein P, Zeller J, Revuz J, et al. Quality-of-life impairment in neurofibromatosis type 1: A cross-sectional study of 128 cases. Archives of Dermatology 2001;137:1421-1425.	Doesn't report a relevant economic evaluation
108	Wolsey DH, Larson SA, Creel D, et al. Can Screening for Optic Nerve Gliomas in Patients With Neurofibromatosis Type I Be Performed With Visual-Evoked Potential Testing? Journal of AAPOS 2006;10:307-311.	Doesn't report a relevant economic evaluation

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109	Wolters PL, Burns KM, Martin S, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. American Journal of Medical Genetics, Part A 2015;167:2103-2113.	Doesn't report a relevant economic evaluation
110	Yamauchi T, Suka M, Nishigori C, et al. Evaluation of neurofibromatosis type 1 progression using a nationwide registry of patients who submitted claims for medical expense subsidies in Japan between 2008 and 2012. Orphanet Journal of Rare Diseases 2019;14 (1) (no pagination).	Doesn't report a relevant economic evaluation
111	Yang X, Desai K, Agrawal N, et al. Treatment, resource use and costs among pediatric patients with neurofibromatosis type 1 and plexiform neurofibromas. Pediatric Health, Medicine and Therapeutics 2020;11:421-428.	Doesn't report a relevant economic evaluation
112	Yifei G, Xiaolong S, Yang L, et al. Clinical outcomes of anterior correction and reconstruction for neurofibromatosis-associated severe cervical kyphotic deformity. International Orthopaedics 2019;43:639-646.	Doesn't report a relevant economic evaluation
113	Zehou O, Ferkal S, Brugieres P, et al. Absence of Efficacy of Everolimus in Neurofibromatosis 1-Related Plexiform Neurofibromas: Results from a Phase 2a Trial. Journal of Investigative Dermatology 2019;139:718-720.	Doesn't report a relevant economic evaluation

Abbreviation: SLR: systematic literature review

Table 70. List of studies excluded in the HRQoL SLR at full-text review and reasoning for exclusion

#	Citation	Reason for exclusion
1	Acarturk TO, Yigenoglu B, Pekedis O. Excision and "transcutaneous" lift in patients with neurofibromatosis of the fronto-temporo-orbital and auricular regions. Journal of Craniofacial Surgery 2009;20:771-4.	Irrelevant study design
2	Afridi SK, Leschziner GD, Ferner RE. Prevalence and clinical presentation of headache in a National Neurofibromatosis 1 Service and impact on quality of life. American Journal of Medical Genetics, Part A 2015;167:2282-2285.	HRQoL not in a PN population (no utility reported)
3	Algermissen B, Muller U, Katalinic D, et al. CO<inf>2</inf> laser treatment of neurofibromas of patients with neurofibromatosis type 1: Five years experience. Medical Laser Application 2001;16:265-274.	Doesn't report HRQoL
4	Avery RA, Hardy KK. Vision specific quality of life in children with optic pathway gliomas. Journal of Neuro-Oncology 2014;116:341-347.	Doesn't report HRQoL
5	Bergqvist C, Servy A, Valeyrie-Allanore L, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet journal of rare diseases 2020;15:37.	Irrelevant study design
6	Bicudo NP, de Menezes Neto BF, da Silva de Avo LR, et al. Quality of Life in Adults with Neurofibromatosis 1 in Brazil. Journal of genetic counseling 2016;25:1063-1074.	Doesn't report HRQoL
7	Bottesi G, Spoto A, Trevisson E, et al. Dysfunctional coping is related to impaired skin-related quality of life and psychological distress in patients with neurofibromatosis type 1 with major skin involvement. British Journal of Dermatology 2020;182:1449-1457.	HRQoL not in a PN population (no utility reported)
8	Brenaut E, Nizery-Guermeur C, Audebert-Bellanger S, et al. Clinical Characteristics of Pruritus in Neurofibromatosis 1. Acta Dermato-Venereologica 2016;96:398-9.	Doesn't report HRQoL
9	Brunt LM, Lairmore TC, Doherty GM, et al. Adrenalectomy for familial pheochromocytoma in the laparoscopic era. Annals of Surgery 2002;235:713-721.	Irrelevant study design
10	Chamseddin BH, Hernandez L, Solorzano D, et al. Robust surgical approach for cutaneous neurofibroma in neurofibromatosis type 1. JCI Insight 2019;4 (11) (no pagination).	HRQoL not in a PN population (no utility reported)
11	Cipolletta S, Spina G, Spoto A. Psychosocial functioning, self-image, and quality of life in children and adolescents with neurofibromatosis type 1. Child: care, health and development 2018;44:260-268.	HRQoL not in a PN population (no utility reported)
12	Cohen JS, Levy HP, Sloan J, et al. Depression among adults with neurofibromatosis type 1: Prevalence and impact on quality of life. Clinical Genetics 2015;88:425-430.	HRQoL not in a PN population (no utility reported)
13	Copley-Merriman C, Yang X, Juniper M, et al. Pro85 Impact of Neurofibromatosis Type 1 and Plexiform Neurofibromas on Patient-Reported Health-Related Quality of Life. Value in Health 2020;23 (Supplement 1):S344.	Irrelevant study design

#	Citation	Reason for exclusion
14	Cosyns M, Mortier G, Janssens S, et al. Voice-related quality of life in adults with neurofibromatosis type 1. Journal of Voice 2012;26:e57-e62.	HRQoL not in a PN population (no utility reported)
15	Coutinho V, Camara-Costa H, Kemlin I, et al. The Discrepancy between Performance-Based Measures and Questionnaires when Assessing Clinical Outcomes and Quality of Life in Pediatric Patients with Neurological Disorders. Applied neuropsychology 2017;Child. 6:255-261.	HRQoL not in a PN population (no utility reported)
16	Dakwar E, Smith WD, Malone KT, et al. Minimally invasive lateral extracavitary resection of foraminal neurofibromas. Journal of Clinical Neuroscience 2011;18:1510-2.	Doesn't report HRQoL
17	Dolan KD, Yuh WT. Gadolinium-enhanced facial nerves: accompanying bilateral acoustic tumors in patient with neurofibromatosis. Annals of Otology, Rhinology & Laryngology 1989;98:747-8.	Irrelevant study design
18	Doser K, Andersen EW, Kenborg L, et al. Clinical characteristics and quality of life, depression, and anxiety in adults with neurofibromatosis type 1: A nationwide study. American Journal of Medical Genetics, Part A 2020;182:1704-1715.	HRQoL not in a PN population (no utility reported)
19	Draucker CB, Nutakki K, Varni JW, et al. The health-related quality of life of children, adolescents, and young adults with neurofibromatosis type 1 and their families: Analysis of narratives. Journal for specialists in pediatric nursing : JSPN 2017;22.	Doesn't report HRQoL
20	Ehara Y, Koga M, Imafuku S, et al. Distribution of diffuse plexiform neurofibroma on the body surface in patients with neurofibromatosis 1. Journal of Dermatology 2020;47:190-192.	Doesn't report HRQoL
21	Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. The Lancet Oncology 2019;20:1011-1022.	Doesn't report HRQoL
22	Farmer JP, Khan S, Khan A, et al. Neurofibromatosis type 1 and the pediatric neurosurgeon: A 20-year institutional review. Pediatric Neurosurgery 2002;37:122-136.	Doesn't report HRQoL
23	Ferner RE, Thomas M, Mercer G, et al. Evaluation of quality of life in adults with neurofibromatosis 1 (NF1) using the Impact of NF1 on Quality Of Life (INF1-QOL) questionnaire. Health and Quality of Life Outcomes 2017;15 (1) (no pagination).	HRQoL not in a PN population (no utility reported)
24	Fisher MJ, Shih CS, Rhodes SD, et al. Cabozantinib for neurofibromatosis type 1-related plexiform neurofibromas: a phase 2 trial. Nat Med 2021;27:165-173.	Doesn't report HRQoL
25	Fjermestad KW, Nyhus L, Kanavin OJ, et al. Health Survey of Adults with Neurofibromatosis 1 Compared to Population Study Controls. Journal of genetic counseling 2018;27:1102-1110.	Doesn't report HRQoL
26	Fjermestad KW. Health complaints and work experiences among adults with neurofibromatosis 1. Occupational medicine (Oxford, England) 2019;69:504-510.	Doesn't report HRQoL

#	Citation	Reason for exclusion
27	Fletcher AN, Schwend RM. The Ecuador Pediatric Spine Deformity Surgery Program: An SRS-GOP Site, 2008-2016. Spine Deformity 2019;7:220-227.	Irrelevant study design
28	Flood TF, Stence NV, Maloney JA, et al. Pediatric brain: Repeated exposure to linear gadolinium-based contrast material is associated with increased signal intensity at unenhanced T1-weighted MR imaging. Radiology 2017;282:222-228.	Irrelevant population
29	Freedman I, Koo A, Yeagle E, et al. Does neurofibromatosis 1 status impact outcomes for pediatric/young adults undergoing spinal fusion? Surgical Neurology International 2020;11 (60) (no pagination).	Doesn't report HRQoL
30	Furlong W, Barr RD, Feeny D, et al. Patient-focused measures of functional health status and health-related quality of life in pediatric orthopedics: A case study in measurement selection. Health and Quality of Life Outcomes 2005;3 (no pagination).	Irrelevant study design
31	Gilboa Y, Rosenblum S, Fattal-Valevski A, et al. Application of the International Classification of Functioning, Disability and Health in children with neurofibromatosis type 1: a review. Developmental Medicine & Child Neurology 2010;52:612-9.	Irrelevant study design
32	Giudice G, Favia G, Tempesta A, et al. Confocal microscopy predicts the risk of recurrence and malignant transformation of mucocutaneous neurofibromas in NF-1: An observational study. Dermatology Research and Practice 2018;2018 (no pagination).	Doesn't report HRQoL
33	Goetsch Weisman A, Haws T, Lee J, et al. Transition Readiness Assessment in Adolescents and Young Adults with Neurofibromatosis Type 1 (NF1). Comprehensive child and adolescent nursing 2020:1-17.	Doesn't report HRQoL
34	Graf A, Landolt MA, Mori AC, et al. Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1. Journal of Pediatrics 2006;149:348-353.	HRQoL not in a PN population (no utility reported)
35	Griffiths S, Thompson P, Frayling I, et al. Molecular diagnosis of neurofibromatosis type 1: 2 Years experience. Familial Cancer 2007;6:21-34.	Doesn't report HRQoL
36	Guiraud M, Bouroubi A, Beauchamp R, et al. Cutaneous neurofibromas: Patients' medical burden, current management and therapeutic expectations: Results from an online European patient community survey. Orphanet Journal of Rare Diseases 2019;14 (1) (no pagination).	HRQoL not in a PN population (no utility reported)
37	Hivelin M, Wolkenstein P, Lepage C, et al. Facial aesthetic unit remodeling procedure for neurofibromatosis type 1 hemifacial hypertrophy: report on 33 consecutive adult patients. Plastic & Reconstructive Surgery 2010;125:1197-207.	Doesn't report HRQoL
38	Holzapfel J, Kandels D, Schmidt R, et al. Favorable prognosis in pediatric brainstem low-grade glioma: Report from the German SIOP-LGG 2004 cohort. International Journal of Cancer 2020;146:3385-3396.	Doesn't report HRQoL
39	Iannicelli E, Rossi G, Almberger M, et al. Integrated imaging in peripheral nerve lesions in type 1 neurofibromatosis. La Radiologia medica 2002;103:332-343.	Doesn't report HRQoL

#	Citation	Reason for exclusion
40	Imperato A CG, Meccariello G. Optic pathway gliomas of the pediatric age: impact of neurosurgery on quality of life. Child's Nervous System 2018;34:1022.	Doesn't report HRQoL
41	Kalakoti P, Missios S, Menger R, et al. Association of risk factors with unfavorable outcomes after resection of adult benign intradural spine tumors and the effect of hospital volume on outcomes: an analysis of 18, 297 patients across 774 US hospitals using the National Inpatient Sample (2002-2011). Neurosurgical focus 2015;39:E4.	Doesn't report HRQoL
42	Kodra Y, Giustini S, Divona L, et al. Health-related quality of life in patients with neurofibromatosis type 1: A survey of 129 Italian patients. Dermatology 2009;218:215-220.	HRQoL not in a PN population (no utility reported)
43	Kondyli M, Larouche V, Saint-Martin C, et al. Trametinib for progressive pediatric low-grade gliomas. Journal of Neuro-Oncology 2018;140:435-444.	Irrelevant study design
44	Kongkriangkai AM, King C, Martin LJ, et al. Substantial pain burden in frequency, intensity, interference and chronicity among children and adults with neurofibromatosis Type 1. American Journal of Medical Genetics, Part A 2019;179:602-607.	Doesn't report HRQoL
45	Krab LC, Oostenbrink R, de Goede-Bolder A, et al. Health-Related Quality of Life in Children with Neurofibromatosis Type 1: Contribution of Demographic Factors, Disease-Related Factors, and Behavior. Journal of Pediatrics 2009;154:420-425.Irrelevant study design.	HRQoL not in a PN population (no utility reported)
46	Kurucan E, Bernstein DN, Thirukumaran C, et al. National Trends in Spinal Fusion Surgery for Neurofibromatosis. Spine Deformity 2018;6:712-718.	Doesn't report HRQoL
47	Kuwahara M, Yurugi S, Iioka H, et al. Problems on resecting the neurofibromatosis type 1 from experiences of 17 patients. [Japanese]. Skin Research 2004;3:591-596.	Doesn't report HRQoL
48	Lantieri L, Grimbert P, Ortonne N, et al. Face transplant: long-term follow-up and results of a prospective open study. The Lancet 2016;388:1398-1407.	Irrelevant study design
49	Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II weekly vinblastine for chemotherapy-naive children with progressive low-grade glioma: A Canadian pediatric brain tumor consortium study. Journal of Clinical Oncology 2016;34:3537-3543.	Doesn't report HRQoL
50	Lundar T, Due-Tonnessen BJ, Egge A, et al. Neurosurgical treatment of pediatric low-grade midbrain tumors: a single consecutive institutional series of 15 patients. Journal of neurosurgery 2014;Pediatrics. 14:598-603.	Irrelevant study design
51	Lyu Q, Zhou C, Song Y, et al. Does spinal deformity correction of non-dystrophic scoliosis in neurofibromatosis type I with one-stage posterior pedicle screw technique produce outcomes similar to adolescent idiopathic scoliosis? Spine Journal 2017;17:1850-1858.	Doesn't report HRQoL
52	Maloney E, Stanescu AL, Perez FA, et al. Surveillance magnetic resonance imaging for isolated optic pathway gliomas: is gadolinium necessary? Pediatric Radiology 2018;48:1472-1484.	Doesn't report HRQoL

#	Citation	Reason for exclusion
53	Marsault P, Ducassou S, Menut F, et al. Diagnostic performance of an unenhanced MRI exam for tumor follow-up of the optic pathway gliomas in children. Neuroradiology 2019;61:711-720.	Doesn't report HRQoL
54	Marsault P, Menut F, Bessou P, et al. Optic pathway gliomas: MRI follow-up including imaging with gadolinium-based contrast agent: Accuracy of non-enhancement sequences for diagnosis of progression. Pediatric Radiology 2019;49 (Supplement 2):S311.	Doesn't report HRQoL
55	Mauger D, Zeller J, Revuz J, et al. Psychological impact of neurofibromatosis type 1: Analysis of interviews with 12 patients to evaluate quality of life. [French]. Annales de Dermatologie et de Venereologie 1999;126:619-620.	Irrelevant study design
56	Merker VL, Bredella MA, Cai W, et al. Relationship between whole-body tumor burden, clinical phenotype, and quality of life in patients with neurofibromatosis. American Journal of Medical Genetics, Part A 2014;164:1431-1437.	HRQoL not in a PN population (no utility reported)
57	Metalwala Z, Okunseri C, Fletcher S, et al. Orthognathic Surgical Outcomes in Patients With and Without Craniofacial Anomalies. Journal of Oral and Maxillofacial Surgery 2018;76:436.Irrelevant study design-436.e8.	Irrelevant population
58	Miraglia E, Calvieri S, Giustini S. Pruritus in neurofibromatosis type 1. Giornale Italiano di Dermatologia e Venereologia 2018;153:120-122.	Doesn't report HRQoL
59	Morandell E, Salandin M, Mantovan F. [Experiences of patients with neurofibromatosis type 1 and their families or caregivers]. Kinderkrankenschwester 2013;32:102-5.	Irrelevant study design
60	Morandell E, Salandin M, Mantovan F. [Experiences of patients with neurofibromatosis type 1 and their families or caregivers]. Kinderkrankenschwester 2013;32:102-5.	Doesn't report HRQoL
61	Muram TM, Stevenson DA, Watts-Justice S, et al. A cost savings approach to SPRED1 mutational analysis in individuals at risk for neurofibromatosis type 1. American Journal of Medical Genetics, Part A 2013;161:467-472.	Irrelevant population
62	Newman WC, Berry-Candelario J, Villavieja J, et al. Improvement in Quality of Life Following Surgical Resection of Benign Intradural Extramedullary Tumors: A Prospective Evaluation of Patient-Reported Outcomes. Neurosurgery 2021.	HRQoL not in a PN population (no utility reported)
63	Nutakki K, Hingtgen CM, Monahan P, et al. Development of the adult PedsQL TM neurofibromatosis type 1 module: initial feasibility, reliability and validity. Health & Quality of Life Outcomes 2013;11:21.	Doesn't report HRQoL
64	Nutakki K, Hingtgen CM, Monahan P, et al. Development of the Adult PedsQLTM Neurofibromatosis Type 1 Module: Initial Feasibility, Reliability and Validity. Health and Quality of Life Outcomes 2013;11 (1) (no pagination).	HRQoL not in a PN population (no utility reported)
65	Nutakki K, Varni JW, Steinbrenner S, et al. Development of the pediatric quality of life inventory neurofibromatosis type 1 module items for children, adolescents and young adults: qualitative methods. Journal of Neuro-Oncology 2017;132:135-143.	Doesn't report HRQoL
66	Nutakki K, Varni JW, Swigonski NL. PedsQL Neurofibromatosis Type 1 Module for children, adolescents and young adults:	HRQoL not in a PN population

#	Citation	Reason for exclusion
	feasibility, reliability, and validity. Journal of Neuro-Oncology 2018;137:337-347.	(no utility reported)
67	Oostenbrink R, Spong K, de Goede-Bolder A, et al. Parental Reports of Health-Related Quality Of Life in Young Children with Neurofibromatosis Type 1: Influence of Condition Specific Determinants. Journal of Pediatrics 2007;151:182-186.Irrelevant population.	Irrelevant study design
68	Pacheco-Cuellar G, Castaneda-Saldana I, Valdez-Andrade J, et al. P-294 Incorporating genetic counseling service into the gastrointestinal tumor board: Experience, obstacles, and opportunities in a Mexican center. Annals of Oncology 2020;31 (Supplement 3):S185-S186.	HRQoL not in a PN population (no utility reported)
69	Page PZ, Page GP, Ecosse E, et al. Impact of neurofibromatosis 1 on quality of life: A cross-sectional study of 176 American cases. American Journal of Medical Genetics, Part A 2006;140:1893-1898.	HRQoL not in a PN population (no utility reported)
70	Payne JM, Barton B, Ullrich NJ, et al. Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1. Neurology 2016;87:2575-2584.	Irrelevant population
71	Reichman M, Riklin E, Macklin E, et al. Virtual mind-body treatment for adolescents with neurofibromatosis: Study protocol for a single-blind randomized controlled trial. Contemporary Clinical Trials 2020;95 (no pagination).	Irrelevant study design
72	Ruegg EM, Hivelin M, Hemery F, et al. Face transplantation program in France: a cost analysis of five patients. Transplantation 2012;93:1166-72.	HRQoL not in a PN population (no utility reported)
72	Saltik S, Basgul SS. [Quality of life in children with neurofibromatosis type 1, based on their mothers' reports]. Turk Psikiyatri Dergisi 2013;24:25-34.	Irrelevant study design
74	Sanagoo A, Jouybari L, Koohi F, et al. Evaluation of QoL in neurofibromatosis patients: A systematic review and meta-analysis study. BMC Neurology 2019;19 (1) (no pagination).	Doesn't report HRQoL
75	Schooler GR, Davis JT, Daldrup-Link HE, et al. Current utilization and procedural practices in pediatric whole-body MRI. Pediatric Radiology 2018;48:1101-1107.	Irrelevant population
76	Shah M, Mavers M, Bree A, et al. Quality of life and depression assessment in nevoid basal cell carcinoma syndrome. International Journal of Dermatology 2011;50:268-76.	Irrelevant population
77	Shin DW, Sohn MJ, Kim HS, et al. Clinical analysis of spinal stereotactic radiosurgery in the treatment of neurogenic tumors. Journal of neurosurgery 2015;Spine. 23:429-437.	HRQoL not in a PN population (no utility reported)
78	Soghi I, Saeedi S, Sanagoo A, et al. Quality of life in a group of Iranian patients with neurofibromatosis type 1 with cutaneous expressions. [Persian]. Journal of Mazandaran University of Medical Sciences 2018;28:95-103.	Irrelevant population
79	Soulier G, van Leeuwen BM, Putter H, et al. Quality of Life in 807 Patients with Vestibular Schwannoma: Comparing Treatment	HRQoL not in a PN population

#	Citation	Reason for exclusion
	Modalities. Otolaryngology - Head and Neck Surgery (United States) 2017;157:92-98.	(no utility reported)
80	Spuijbroek AT, Oostenbrink R, Landgraf JM, et al. Health-related quality of life in preschool children in five health conditions. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:779-786.	Irrelevant study design
81	Tora MS, Xenos D, Texakalidis P, et al. Treatment of neurofibromatosis 1-associated malignant peripheral nerve sheath tumors: a systematic review. Neurosurgical Review 2020;43:1039-1046.	Doesn't report HRQoL
82	Tsang E, Birch P, Friedman JM. Valuing gene testing in children with possible neurofibromatosis 1. Clinical Genetics 2012;82:591-593.	Doesn't report HRQoL
83	Turkson L, Mamuszka H, Grimshaw K, et al. Abstract 5288: MPNST treatment and diagnosis in NF1: A health economic model. Cancer Research 2018;78:5288.	Doesn't report HRQoL
84	Van Der Vaart T, Rietman AB, Plasschaert E, et al. Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology 2016;86:154-160.	HRQoL not in a PN population (no utility reported)
85	Vardarinos A, Zafeiriou DI, Vargiami E, et al. Parental reports of health-related quality of life in greek children with neurofibromatosis type 1. Journal of Pediatrics 2009;155:453.	HRQoL not in a PN population (no utility reported)
86	Varni JW, Nutakki K, Swigonski NL. Cognitive functioning and pain interference mediate pain predictive effects on health-related quality of life in pediatric patients with Neurofibromatosis Type 1. European Journal of Paediatric Neurology. 2020.	HRQoL not in a PN population (no utility reported)
87	Varni JW, Nutakki K, Swigonski NL. Pain, skin sensations symptoms, and cognitive functioning predictors of health-related quality of life in pediatric patients with Neurofibromatosis Type 1. Quality of Life Research 2019;28:1047-1052.	HRQoL not in a PN population (no utility reported)
88	Varni JW, Nutakki K, Swigonski NL. Speech difficulties and patient health communication mediating effects on worry and health-related quality of life in children, adolescents, and young adults with Neurofibromatosis Type 1. American Journal of Medical Genetics, Part A 2019;179:1476-1482.	HRQoL not in a PN population (no utility reported)
89	Vassallo G, Mughal Z, Robinson L, et al. Perceived fatigue in children and young adults with neurofibromatosis type 1. Journal of Paediatrics & Child Health 2020;56:878-883.	Irrelevant study design
90	Vranceanu AM, Merker VL, Park E, et al. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: A systematic review of the literature. Journal of Neuro-Oncology 2013;114:257-262.	Irrelevant study design
91	Vranceanu AM, Merker VL, Park ER, et al. Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature. Journal of Neuro Oncology. 2015;07.	HRQoL not in a PN population (no utility reported)
92	Wang J, Liu C, Wang C, et al. Early and Midterm Outcomes of Surgical Correction for Severe Dystrophic Cervical Kyphosis in	Doesn't report HRQoL

#	Citation	Reason for exclusion
	Patients with Neurofibromatosis Type 1: A Retrospective Multicenter Study. World Neurosurgery 2019;127:Irrelevant study design190-Irrelevant study design200.	
93	Wiener L, Battles H, Bedoya SZ, et al. Identifying Symptoms of Distress in Youth Living with Neurofibromatosis Type 1 (NF1). Journal of Genetic Counseling 2018;27:115-123.	Doesn't report HRQoL
94	Wolkenstein P, Durand-Zaleski I, Moreno JC, et al. Cost evaluation of the medical management of neurofibromatosis 1: A prospective study on 201 patients. British Journal of Dermatology 2000;142:1166-1170.	HRQoL not in a PN population (no utility reported)
95	Wolkenstein P, Loundou A, Barrau K, et al. Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. Journal of the American Academy of Dermatology 2007;56:621-3.	HRQoL not in a PN population (no utility reported)
96	Wolkenstein P, Zeller J, Revuz J, et al. Quality-of-life impairment in neurofibromatosis type 1: A cross-sectional study of 128 cases. Archives of Dermatology 2001;137:1421-1425.	Doesn't report HRQoL
97	Wolsey DH, Larson SA, Creel D, et al. Can Screening for Optic Nerve Gliomas in Patients With Neurofibromatosis Type I Be Performed With Visual-Evoked Potential Testing? Journal of AAPOS 2006;10:307-311.	Doesn't report HRQoL
98	Yamauchi T, Suka M, Nishigori C, et al. Evaluation of neurofibromatosis type 1 progression using a nationwide registry of patients who submitted claims for medical expense subsidies in Japan between 2008 and 2012. Orphanet Journal of Rare Diseases 2019;14 (1) (no pagination).	Doesn't report HRQoL
99	Yang X, Desai K, Agrawal N, et al. Treatment, resource use and costs among pediatric patients with neurofibromatosis type 1 and plexiform neurofibromas. Pediatric Health, Medicine and Therapeutics 2020;11:421-428.	Doesn't report HRQoL
100	Yifei G, Xiaolong S, Yang L, et al. Clinical outcomes of anterior correction and reconstruction for neurofibromatosis-associated severe cervical kyphotic deformity. International Orthopaedics 2019;43:639-646.	Doesn't report HRQoL

Abbreviations: HRQoL: health related quality of life; SLR: systematic literature review

17.5 Appendix 5: Economic SLR study extractions

17.5.1 HRQoL study extractions

Table 71. HRQoL study extractions

<table>
<tr><th>Source</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr>
<td>Gross 2020[18, 134]</td>
<td>Patients
Children aged 2–18 years with a clinical diagnosis of NF1, who had inoperable, measurable PN.

Patients with at least one NF-related complication were enrolled.

Population characteristics (n=50)
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Female (n)</td><td>20</td></tr>
<tr><td>Male (n)</td><td>30</td></tr>
<tr><td colspan="2">Age (years)</td></tr>
<tr><td>Median</td><td>10.2</td></tr>
<tr><td>Range</td><td>3.5–17.4</td></tr>
<tr><td colspan="2">Target NF volume (mL)</td></tr>
<tr><td>Median</td><td>487</td></tr>
<tr><td>Range</td><td>5–3820</td></tr>
<tr><td colspan="2">NF progression status at entry (n)</td></tr>
<tr><td>Progressive</td><td>21</td></tr>
<tr><td>Nonprogressive</td><td>15</td></tr>
<tr><td>Insufficient data</td><td>14</td></tr>
<tr><td colspan="2">NF-related complications,* n (%)</td></tr>
</table>
</td>
<td>US; outpatient paediatric oncology clinic.</td>
<td>N=50 (study population).

Of the study population, evaluable HRQoL data was available for children (n=29) and parents (n=45).</td>
<td>HRQoL reported for patients with NF1 and PN.

HRQoL was assessed at baseline and after 12 months of treatment of selumetinib (pre-cycle 13).</td>
<td>The PedsQL scales measured patient HRQoL.

For patients with an NF-related motor complication, PROMIS Mobility and Upper Extremity short forms were used to assess physical functioning.</td>
<td>PedsQL
Table 1. Self-reported PedsQL scores
<table>
<tr><th rowspan="2">Domain</th><th colspan="2">Mean (range)</th><th rowspan="2">Mean (95% CI) difference (n=29)</th></tr>
<tr><th>Baseline (n=33)</th><th>12 months (n=29)</th></tr>
<tr><td>Total</td><td>73.9 (13.0–96.7)</td><td>79.6 (30.4–100.0)</td><td>6.7 (0.1,13.3)</td></tr>
<tr><td>Physical</td><td>75.4 (15.6–100.0)</td><td>80.9 (21.9–100.0)</td><td>6.7 (0.0, 15.6)</td></tr>
<tr><td>Emotional</td><td>75.9 (5.0–100.0)</td><td>83.3 (45.0–100.0)</td><td>7.4 (-2.7,17.5)</td></tr>
<tr><td>Social</td><td>75.9 (0–100.0)</td><td>80.5 (15.0–100.0)</td><td>5.2 (-3.5, 13.9)</td></tr>
<tr><td>School*</td><td>66.3 (10.0–100.0)</td><td>70.6 (0–100.0)</td><td>5.0 (-2.2, 12.2)</td></tr>
</table>
*n=28 (baseline); n=25 (12 months), n=23 (mean difference)
Abbreviations: CI: confidence interval; PedsQL: Pediatric Quality of Life Inventory

Table 2. Parent-reported PedsQL scores
<table>
<tr><th rowspan="2">Domain</th><th colspan="2">Mean (range)</th><th rowspan="2">Mean (95% CI) difference (n=45)</th></tr>
<tr><th>Baseline (n=50)</th><th>12 months (n=45)</th></tr>
</table>
</td>
<td>Consistency with NICE reference case:
No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis.

The similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.</td>
</tr>
</table>

						For all scales, child-reported scores are for children aged ≥8 years, and parent-reported scores are for children aged ≥5 years, except for PedsQL, for which parent-reported scores are for children aged ≥2 years.		**Relevance to the decision problem:** Patients included were paediatric and had NF1 with symptomatic, inoperable PN, fully aligned with the decision problem.

Disfigurement	44(88)
Motor dysfunction	33(66)
Pain	26 (52)
Airway	16(32)
Vision	10 (20)
Bowel/bladder	10 (20)
Other	11(22)

*Average number of NF-related complications = 3 (range 1–5)
Abbreviations: NF: neurofibroma

Intervention
Selumetinib,
25 mg/m^2, every 12 hours, 28 day cycles.

Comparator
None.

Recruitment
No details of recruitment or enrolment provided.

Total	60.8 (20.7–98.9)	73.3 (39.1–98.9)	13.0 (8.1,17.8)
Physical	60.6 (9.4–100.0)	73.2 (18.8–100.0)	13.8 (7.8,19.8)
Emotional	64.9 (15.0–100.0)	82.2 (40.0–100.0)	17.4 (11.1, 23.8)
Social	57.9 (10.0–100.0)	69.7 (20.0–100.0)	11.7 (5.0,18.5)
School*	60.8 (8.3–95.0)	67.1 (20.0–100.0)	6.0 (-0.5,12.6)

*n=44 (baseline); n=40 (12 months), n=37 (mean difference)
Abbreviations: CI: confidence interval; PedsQL: Pediatric Quality of Life Inventory

PROMIS Mobility and Upper Extremity Scales
Table 3. Self-reported PROMIS scores

Domain	Mean (range)		Mean (95% CI) difference
	Baseline	12 months	
Mobility*	46.6 (32.3–58.5)	48.0 (38.3–58.5)	1.8 (-1.4, 5.1)
Upper Extremity**	46.0 (20.4–56.7)	47.4 (25.5–56.7)	1.6 (-1.7, 4.9)

*n=23 (baseline); n=20 (12 months), n=20 (mean difference)
** n=22 (baseline); n=20 (12 months), n=19 (mean difference)
Abbreviations: CI: confidence interval; PROMIS: Patient-Reported Outcomes Measurement Information System

Table 4. Parent-reported PROMIS scores

<table>
<tr><th>Source</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><th rowspan="2">Domain</th><th colspan="2">Mean (range)</th><th rowspan="2">Mean (95% CI) difference</th></tr>
<tr><th>Baseline</th><th>12 months</th></tr>
<tr><td>Mobility*</td><td>37.4 (19.8 – 56.5)</td><td>41.1 (21.1– 56.5)</td><td>3.0 (1.3, 4.7)</td></tr>
<tr><td>Upper Extremity*</td><td>38.1 (14.0 – 54.8)</td><td>40.6 (14.0– 54.8)</td><td>1.8 (-0.7, 4.4)</td></tr>
</table>
*n=32 (baseline); n=29 (12 months), n=28 (mean difference)
** n=31 (baseline); n=29 (12 months), n=27 (mean difference)
Abbreviations: CI: confidence interval; PROMIS: Patient-Reported Outcomes Measurement Information System</td><td></td></tr>
<tr><td>Hamoy-Jimenez 2020[152]</td><td>Patients
All adult patients met the clinical diagnostic criteria for NF1 and/or had genetically confirmed NF1.

Population characteristics
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Female</td><td>57%</td></tr>
<tr><td>Male</td><td>43%</td></tr>
<tr><td>Mean age</td><td>33 (SD 13.5)</td></tr>
<tr><td>Known PN</td><td>39%</td></tr>
<tr><td>History of MPNST</td><td>9%</td></tr>
<tr><td>Optic glioma</td><td>15%</td></tr>
</table></td><td>Canada, academic clinic.</td><td>N=162

Response rate not reported.</td><td>Not Reported.</td><td>HSUV were assessed using the EQ-5D-5L. A Canadian valuation algorithm was used to estimate utility scores.[153]</td><td>EQ-5D-5L
Mean (SD) utility score: 0.73 (0.24).</td><td>Consistency with NICE reference case: Health utility values were elicited using the EQ-5D-5L, in line with the NICE preference.

The study took place in Canada, and valued utilities using a Canadian value set, which</td></tr>
</table>

Source	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	Ablon's index (median) | 2 (range 1–3) **Abbreviations**: SD: standard deviation Recruitment Patients attending the Elisabeth Raab Neurofibromatosis Multidisciplinary Clinic at Toronto General Hospital, between January 2016 and December 2017 were invited to participate.				The study was cross-sectional; therefore, patients were assessed at one timepoint only.		may not be directly relevant to clinical practice in the UK. **Relevance to the decision problem:** The study included patients with NF1, relevant to the decision problem. However, not all patients had PN, and it was unclear if PN were inoperable and symptomatic, which deviates from the decision problem.
Lai 2019[25]	Patients Eligible patients were ages 8—17 years old, had a confirmed diagnosis of NF1, had at least one PN in any location (symptomatic/ asymptomatic) and were fluent in English. **Table 1. Population characteristics**	US	Data from 140 children with NF1 PN were analysed. Response rate is not reported.	HRQoL reported for total patient population, all had NF1 with PN.	HRQoL was assessed using PROMIS, which was completed by the patient.	**Table 2. PROMIS scores reported by patient** **Domain** | **Mean (SD)** | **95% CI** Anxiety | 53.2 (12.2) | 51.2–55.2 Depressive symptoms | 53.5 (12.2) | 51.5–55.6 Fatigue | 50.2 (14.0) | 47.9–52.6	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that

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<tr>
<td></td>
<td>
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Mean age (SD)(years)</td><td>12.53 (2.7)</td></tr>
<tr><td>Female (%)</td><td>35.71</td></tr>
<tr><td>Male (%)</td><td>64.29</td></tr>
<tr><td>White (%)</td><td>64.29</td></tr>
<tr><td>Black/African American</td><td>30.00</td></tr>
<tr><td colspan="2">Age at diagnosis (years)</td></tr>
<tr><td><5</td><td>57.14</td></tr>
<tr><td>5–9</td><td>26.43</td></tr>
<tr><td>10–17</td><td>16.43</td></tr>
<tr><td colspan="2">Café-au-lait spots</td></tr>
<tr><td>No</td><td>0.71</td></tr>
<tr><td>≤6</td><td>12.86</td></tr>
<tr><td>6–20</td><td>48.57</td></tr>
<tr><td>>20</td><td>37.86</td></tr>
<tr><td colspan="2">pNFs</td></tr>
<tr><td>No</td><td>4.29</td></tr>
<tr><td>1</td><td>39.29</td></tr>
<tr><td>1–5</td><td>42.86</td></tr>
<tr><td>≥5</td><td>6.43</td></tr>
<tr><td>Don’t know/unsure</td><td>7.15</td></tr>
<tr><td colspan="2">Chronic itching</td></tr>
<tr><td>No</td><td>58.57</td></tr>
</table>
</td>
<td></td>
<td></td>
<td>HRQoL for adverse events were not reported.</td>
<td>HRQoL was also assessed using the NeuroQoL questionnaire.</td>
<td>
<table>
<tr><td>Meaning and purpose</td><td>40.1 (7.7)</td><td>38.7–41.5</td></tr>
<tr><td>Mobility</td><td>40.9 (9.8)</td><td>39.2–42.5</td></tr>
<tr><td>Pain interference</td><td>49.8 (13.4)</td><td>47.5–52.0</td></tr>
<tr><td>Peer relationship</td><td>43.0 (9.1)</td><td>41.5–44.6</td></tr>
<tr><td>Positive affect and well-being</td><td>46.4 (7.6)</td><td>45.1–47.7</td></tr>
<tr><td>Psychological stress response</td><td>56.8 (9.8)</td><td>55.1–58.5</td></tr>
<tr><td>Upper extremity function</td><td>39.7 (12.4)</td><td>37.6–41.9</td></tr>
</table>
Abbreviations: CI: confidence interval; PROMIS: Patient-Reported Outcomes Measurement Information System; SD: standard deviation

NeuroQoL
Mean (SD) stigma score 53.3 (8.0).
</td>
<td>could be used to generate utility values to inform the cost-effectiveness analysis.

The similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.

Relevance to the decision problem:
Patients included were paediatric and had NF1 with inoperable and progressive PN, aligned with the decision problem.</td>
</tr>
</table>

Source	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	<table><tr><td>Yes</td><td>38.57*</td></tr><tr><td>Unsure</td><td>2.86</td></tr><tr><td colspan="2">Pain</td></tr><tr><td>No</td><td>32.86</td></tr><tr><td>Yes</td><td>67.14</td></tr></table> *37.04% received treatment for chronic itching **Abbreviations**: pNF: neurofibromatosis type 1-related plexiform neurofibromas; SD: standard deviation <u>Recruitment</u> Participants were recruited from three sources: 1. CTF NF Patient Registry (NF registry) 2. Regional NF1 organisations, by posting the invitation to participate on their websites and their social media communication channels 3. The Ann & Robert H. Lurie Children's Hospital of Chicago by placing study flyers in the clinic and mailing invitation letters to eligible patients						However, both symptomatic and asymptomatic patients were included which does not align with the decision problem.

<table>
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<tr>
<td>Ren 2020[154]</td>
<td><u>Patients</u>
Eligible patients were three years or older and had a diagnosis of NF1 PN, mix of craniofacial and non-craniofacial PNs.

The diagnosis of NF1 was made according to NIH criteria by two experienced specialists. All patients underwent biopsy of the tumour to be further confirmed as neurofibromas by pathology, and PNs were predicated by the specialists considering the pathological characteristics and its manifestations.

<u>Population characteristics</u>
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Age range (years)</td><td>3–49</td></tr>
<tr><td>Craniofacial PN (n)</td><td>15</td></tr>
<tr><td>Non-craniofacial PN</td><td>12</td></tr>
<tr><td>Mean age craniofacial patients (years)</td><td>20.0</td></tr>
<tr><td>Mean age non-craniofacial patients (years)</td><td>23.0</td></tr>
<tr><td>Male craniofacial patients (n, %)</td><td>6, 40.0</td></tr>
</table>
</td>
<td>China</td>
<td>N=27

Response rate is not reported.</td>
<td>HRQoL for NF1 patients with craniofacial or non-craniofacial PNs was reported.</td>
<td>HRQoL was measured using the INF1-QOL questionnaire.</td>
<td>Table 1. Total INF1-QOL Scores
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>95% CI</th><th>Median</th></tr>
<tr><td>Total score craniofacial patients</td><td>6.47</td><td>3.8</td><td>4.34–8.59</td><td>6</td></tr>
<tr><td>Total score non-craniofacial patients</td><td>6.42</td><td>3.4</td><td>4.26–8.57</td><td>6</td></tr>
</table>
Abbreviations: CI: confidence interval; INF1-QOL: Impact of NF1 on Quality of Life; SD: standard deviation

Table 2. Single item scores INF1-QOL
<table>
<tr><th>Item</th><th>No problem, n (%)</th><th>Mild problem, n (%)</th><th>Moderate problem, n (%)</th><th>Severe problem, n (%)</th></tr>
<tr><td>Vision</td><td>17 (63.0)</td><td>7 (25.9)</td><td>3 (11.1)</td><td>0 (0)</td></tr>
<tr><td>Cosmetic appearance</td><td>8 (29.6)</td><td>12 (44.4)</td><td>5 (18.5)</td><td>2 (7.4)</td></tr>
<tr><td>Pain quality</td><td>12 (44.4)</td><td>11 (40.7)</td><td>4 (14.8)</td><td>0 (0)</td></tr>
<tr><td>Pain intensity</td><td>11 (40.7)</td><td>9 (33.3)</td><td>5 (18.5)</td><td>2 (7.4)</td></tr>
</table>
</td>
<td>Consistency with NICE reference case:
No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis.

The study took place in China, which may not be directly relevant to clinical practice in the UK.

Relevance to the decision problem: Patients included were NF1 patients with PN, so is aligned to the decision problem; however this study</td>
</tr>
</table>

	Male non-craniofacial patients (n, %)	3, 25.0						Learning problems	17 (63.0)	8 (29.6)	2 (7.4)	0 (0)	included adults and children, limiting its applicability. It is also unclear whether all PNs are inoperable and symptomatic, which may further limit relevance to the decision problem.
	Female craniofacial patients (n, %)	9, 60.0						Behaviour and personality	22 (81.5)	4 (14.8)	1 (3.7)	0 (0)	
	Female non-craniofacial patients (n, %)	9, 75.0						Mobility and walking	15 (55.6)	10 (37.0)	2 (2.7)	0 (0)	
	cNFs ≥50 craniofacial patients (n, %)[a]	7, 46.7						Weakness, numbness, clumsiness in hands	22 (81.5)	5 (18.5)	0 (0)	0 (0)	
	cNFs <50 craniofacial patients (n, %)[a]	8, 53.3						Speech	22 (81.5)	5 (18.5)	0 (0)	0 (0)	
	cNFs ≥50 non-craniofacial patients (n, %)[a]	3, 25.0						Bones	17 (63.0)	9 (33.3)	1 (3.7)	0 (0)	
	cNFs <50 non-craniofacial patients (n, %)[a]	9, 75.0						Breathing	24 (88.9)	3 (11.1)	0 (0)	0 (0)	
	Familial inheritance craniofacial patients (n,%)	8, 53.3						Sleeping	22 (81.5)	5 (18.5)	0 (0)	0 (0)	
	Sporadic inheritance craniofacial patients (n,%)	7, 46.7						Role and outlook on life	16 (59.3)	3 (11.1)	7 (25.9)	1 (3.7)	
	Familial inheritance non-craniofacial patients (n,%)	4, 33.3						Depression and anxiety	21 (77.8)	4 (14.8)	2 (7.4)	0 (0)	
	Sporadic inheritance non-craniofacial patients (n,%)	8, 66.7						**Abbreviations**: INF1-QOL: Impact of NF1 on Quality of Life Questionnaire					
	With other complications craniofacial patients (n,%)[b]	9, 60.0											
	Without other complications craniofacial patients (n,%)[b]	6, 40.0											

Source	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	With other complications non-craniofacial patients (n,%)[b] 4, 33.0 Without other complications non-craniofacial patients (n,%)[b] 8, 66.7 [a]The number of cNFs (diameter >5mm) were recorded [b]Complications included decrease/loss of vision and hearing, bone invasions and dysplasia **Abbreviations**: cNFs: cutaneous neurofibromas; PN: plexiform neurofibromas Recruitment All patients were inpatients and outpatients from the Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine between August 2018 and January 2019						
Rosser 2018[155]	Patients NF1 patients with symptomatic and inoperable PNs, aged >16 years. Population characteristics	US	38 patients. Response rate not reported.	HRQoL reported for whole population, all	HRQoL was assessed using the NF1 PedsQL.	**NF1 PedsQL, mean total functioning score (SD):** 68.1 (19.6).	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus

<table>
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<tr><td></td><td>
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Males (n)</td><td>20</td></tr>
<tr><td>Females (n)</td><td>18</td></tr>
<tr><td>Median age (years)</td><td>23</td></tr>
<tr><td>Age range (years)</td><td>16–39</td></tr>
<tr><td>Tumour visibility, mild (%)*</td><td>40</td></tr>
<tr><td>Tumour visibility, moderate (%)*</td><td>47</td></tr>
<tr><td>Tumour visibility, severe (%)*</td><td>13</td></tr>
<tr><td>NF1 symptoms, mild (%)*</td><td>26</td></tr>
<tr><td>NF1 symptoms, moderate (%)*</td><td>50</td></tr>
<tr><td>NF1 symptoms, severe (%)*</td><td>24</td></tr>
</table>
*Patients rated own disease visibility and symptom severity on a scale of mild, moderate, or severe
Abbreviations: NF1: neurofibromatosis type 1

<u>Recruitment</u>
This patient population is from two clinical trials (NCT02101736 and NCT02096471) before</td><td></td><td></td><td>had NF1 with inoperable PN.

HRQoL for specific health states or adverse events not reported.</td><td>HRQoL was assessed at one timepoint, before receiving treatment.</td><td></td><td>no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis.

The similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.

Relevance to the decision problem: Patients included were NF1 patients with inoperable and symptomatic PN, so is aligned to the</td></tr>
</table>

<table>
<tr><th>Source</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr><td></td><td>receiving treatment. Details of recruitment are not reported.</td><td></td><td></td><td></td><td></td><td></td><td>decision problem; however the study included adults as well as children, limiting the applicability to the decision problem.</td></tr>
<tr><td>Weiss 2014 (NCT00634270)[176]</td><td><u>Patients</u>
Age ≥3 years with a diagnosis of NF1 and an unresectable PN with the potential to cause significant morbidity. Patients evaluated did not have evidence of progressive PNs.

Histologic confirmation of the tumour was not necessary in the presence of consistent clinical and imaging findings.

Other eligibility criteria included adequate performance status (Lansky score of 50 or more), normal blood count and renal, liver, and cardiac function.

<u>Population characteristics</u>
<table><tr><th>Characteristic</th><th>Value</th></tr><tr><td>Female, n (%)</td><td>5 (38.5)</td></tr></table></td><td>US</td><td>Of the 13 patients enrolled, nine were evaluated by self-reported HRQoL questionnaires.

This included six children (mean age: 11.0 years) and three adults (mean age: 29.3 years).</td><td>HRQoL was reported for the patient population, all had NF1 with an unresectable PN.

HRQoL for adverse events were not reported.</td><td>PedsQL 4.0: HRQoL was assessed using the self-report form for children, and proxy form for parents.

FACT-G: HRQoL of adult patients was assessed using the FACT-G</td><td><u>PedsQL 4.0</u>

Table 1. Total scores, child reported (n=6)
<table><tr><td>Baseline</td><td>60.15</td></tr><tr><td>Course six</td><td>71.56</td></tr><tr><td>Mean change</td><td>11.41*</td></tr></table>*p=0.14

Table 2. Emotional domain scores, child reported (n=6)
<table><tr><td>Baseline</td><td>55.83</td></tr><tr><td>Six months</td><td>74.17</td></tr><tr><td>Mean change</td><td>18.33</td></tr></table>*p=0.0354

Table 3.“School” domain scores, child reported (n=6)
<table><tr><td>Baseline</td><td>52.50</td></tr><tr><td>Six months</td><td>69.17</td></tr></table></td><td>Consistency with NICE reference case:
No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis.
The similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK</td></tr>
</table>

Source	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	<table><tr><td>Male, n (%)</td><td>8 (61.5)</td></tr><tr><td>Age (years)</td><td></td></tr><tr><td>Mean (range)</td><td>16 (3–35)</td></tr><tr><td>Race</td><td></td></tr><tr><td>White, n (%)</td><td>10 (76.9)</td></tr><tr><td>Black/ African American, n (%)</td><td>2 (15.4)</td></tr><tr><td>Asian, n (%)</td><td>1 (7.7)</td></tr></table> Intervention Sirolimus; 0.8 mg/m^2, oral, twice/day, followed by subsequent pharmacokinetically guided dosing to achieve a trough blood concentration of 10–15 ng/ml. Recruitment Patients were enrolled at one of nine Department of Defence funded NF Clinical Consortium sites.		The parents of the children also reported on their child's QoL.		questionnaire. All QoL measures were assessed at baseline and after six courses of sirolimus therapy.	<table><tr><td>Mean change</td><td>16.67</td></tr></table>*p=0.0055 **Table 4. Physical domain scores, child reported (n=6)** <table><tr><td>Baseline</td><td>68.75</td></tr><tr><td>Six months</td><td>79.17</td></tr><tr><td>Mean change</td><td>10.42</td></tr></table>*p=0.2545 **Table 5. Social domain scores, child reported (n=6)** <table><tr><td>Baseline</td><td>58.33</td></tr><tr><td>Six months</td><td>59.17</td></tr><tr><td>Mean change</td><td>0.83</td></tr></table>*p=0.9669 **Table 6. Total scores, parent proxy (n=6)** <table><tr><td>Baseline</td><td>63.10</td></tr><tr><td>Course six</td><td>61.23</td></tr><tr><td>Mean change</td><td>-1.88*</td></tr></table>*p=0.5108 FACT-G (adults only) Change in mean scores from baseline to course six (45.33 to 41.47; p=0.2264).	mean the study is anticipated to be applicable to clinical practice in England. **Relevance to the decision problem:** Patients included paediatric and adult patients with NF1 and inoperable PN. It is unclear whether the patients were symptomatic. As such the study is not aligned to the decision problem.

Source	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
Wideman 2014 (NCT00021541)[41]	Patients Children and young adults ≥3 and ≤25 years with a clinical diagnosis of NF1 and unresectable, measurable, progressive PNs with the potential to cause significant morbidity. Patients who underwent prior surgery for their progressive PNs were eligible provided the residual tumour was measurable. Key eligibility criteria: Measurable, progressive PN (≥3 cm in one dimension; ≥20% increase in volume, or ≥13% increase in 2D/≥ 6% increase in 1D measurement over last two consecutive MRI scans); recovered from prior therapy to grade ≤1 organ function toxicity; ECOG PS 0–2; ANC ≥1,500/μL; Hb ≥9.0 g/dL; Platelet count ≥150,000/μL; ALT ≤2xULN; age-adjusted normal serum creatinine. Population characteristics	US	A total of 60 patients with NF1 and PN. 31 and 29 patients were randomised to receive tipifarnib and placebo, respectively. Response rate was not reported, HRQoL data was given for 35 patients at baseline (tipifarnib n=17,	HRQoL reported for patient population, all had NF1 with inoperable PN. HRQoL was reported at baseline, pre-cycle four, seven, and ten, and then after every six cycles. HRQoL for	IPI Scale Parent total scores for participants on placebo were compared with scores for participants receiving tipifarnib	IPI score: pre-cycle four **Tipifarnib (n=17):** Mean score: 3.91 (p vs. baseline=0.015). Mean emotional functioning domain score: 3.72 (p vs. baseline=0.002). **Placebo (n=18):** Mean score: 3.68 (p vs. baseline=0.66). Mean emotional functioning domain score: 3.64 (p vs. baseline=0.99). IPI score: pre-cycle ten **Tipifarnib (n=16):** Mean score: 3.84 (p vs. baseline=0.03). **Placebo (n=12):** Mean score: 3.84 (p vs. baseline=0.11).	**Consistency with NICE reference case:** No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis. The similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England. **Relevance to the decision**

	<table><tr><th>Characteristic</th><th>Placebo</th><th>Tipifarnib</th></tr><tr><td>Median age (years)</td><td>8.2</td><td>9.7</td></tr><tr><td>Age range (years)</td><td>3–17</td><td>3–21.5</td></tr><tr><td>Male (n)</td><td>14</td><td>21</td></tr><tr><td>Female (n)</td><td>15</td><td>10</td></tr><tr><td>IPI Scale mean score</td><td>3.70</td><td>3.69</td></tr><tr><td>IPI emotional functioning subscale mean score</td><td>3.63</td><td>3.37</td></tr><tr><td colspan="3">ECOG PS</td></tr><tr><td>0</td><td>24</td><td>21</td></tr><tr><td>1</td><td>4</td><td>9</td></tr><tr><td>2</td><td>1</td><td>1</td></tr><tr><td>PNs</td><td>52</td><td>44</td></tr><tr><td>Target PNs*</td><td>31</td><td>32</td></tr><tr><td colspan="3">Volume (mL)</td></tr><tr><td>Median**</td><td>316</td><td>572</td></tr><tr><td>Range</td><td>39.6–4,896</td><td>20.5–5,573</td></tr></table> *PN chosen for volumetric MRI analysis to determine time to progression. **PN volume larger in tipifarnib group compared with placebo (p=0.09)		placebo n=18) and 28 pre-cycle ten (tipifarnib n=16, placebo n=12). 35 patients' parents (placebo n=18, tipifarnib (n=17) responded to the HRQoL questionnaire.	adverse events were not reported.			**problem:** Patients included were NF1 patients with inoperable PN; however, the study included adults and paediatric patients, and is unclear whether PN are symptomatic, limiting the applicability to the decision problem.

<table>
<tr><th>Source</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr><td></td><td>Abbreviations: ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; PNs: Plexiform neurofibromas

<u>Intervention</u>
Tipifarnib, 200 mg/m2 orally every 12 h, for 21 days followed by seven days’ rest.

Placebo, same regimen as intervention.

<u>Recruitment</u>
Clinical trial (NCT00021541) included ten participating sites, of which seven enrolled participants.</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Wolkenstein 2009[157]</td><td><u>Patients</u>
Records from families with at least one child aged between eight and 16 years.

<u>Population characteristics</u><table><tr><th>Characteristic</th><th>Value</th></tr><tr><td>Male/female ratio</td><td>1:1</td></tr><tr><td>Mean age (years), ± SD</td><td>12.1 ± 2.6</td></tr></table></td><td>France</td><td>140 families were contacted, and 79 (56%) returned the questionnaires. CDLQI questionn</td><td>HRQoL was assessed for NF1 patients with and without PN. Results from patients</td><td>HRQoL was assessed using the French version of the CDLQI.</td><td>Table 2. CDLQI scores for patients with PN (n=5)<table><tr><th>Dimension</th><th>Score</th><th>Impairment compared to patients without PNs (n=68)</th></tr><tr><td>Symptoms and feelings, mean (SD)*</td><td>26.7 (11.3)</td><td>p=0.005</td></tr></table></td><td>Consistency with NICE reference case:
No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform</td></tr>
</table>

Source	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	<table><tr><td>More than 2 PNs (n=76), n (%)</td><td>5 (7)</td></tr><tr><td>Orthopaedic manifestations, n (%)</td><td>26 (33)</td></tr><tr><td>Dysmorphic features, n (%)</td><td>14 (18)</td></tr><tr><td>Hydrocephalus, n (%)</td><td>3 (4)</td></tr><tr><td>Learning difficulties, n (%)</td><td>54 (68)</td></tr><tr><td>Optic pathway glioma (n=64), n (%)</td><td>18 (28)</td></tr><tr><td>CDLQI score, mean ± SD**</td><td>3.4 ± 3.0 (11.3 ± 10.1)</td></tr></table> **Abbreviations**: CDLQI: Children's Dermatology Life Quality Index; PN: plexiform neurofibroma; SD: standard deviation <u>Recruitment</u> Recruitment occurred via mail in November 2005.		aire scores were available from 75 children, of whom five had NF1 with PN.	with PN are presented here. HRQoL for specific adverse events are not reported.		<table><tr><td>School or holidays, mean (SD)[a]</td><td>20.0 (13.3)</td><td>p=0.007</td></tr></table> [a]The scores are presented as a percentage of the maximum possible score **Abbreviations**: CDLQI: Children's Dermatology Life Quality Index; PN: plexiform neurofibroma; SD: standard deviation	the cost-effectiveness analysis. The study took place in France, which may not be directly relevant to clinical practice in the UK. **Relevance to the decision problem:** The patients considered have NF1 and PN and are paediatric patients, so are relevant to the decision problem. However, it is unclear whether the PNs are inoperable and symptomatic, limiting relevance to the decision problem.

<table>
<tr><th>Source</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr>
<td>Wolters 2015[19]</td>
<td><u>Patients</u>
Children and adolescents six to 18 years of age with NF1 and PN.

Patients were enrolled from a natural history protocol study at the NCI.

Eligibility criteria included diagnosis of NF1 according to the NIH Consensus Conference criteria or a confirmed NF1 germline mutation with analysis performed in a CLIA-certified laboratory.

<u>Population characteristics</u>
<table>
<tr><th>Characteristic</th><th>Value (all included patients) N=60</th><th>Value (Adolescent patients [10—18 years]) N=42</th></tr>
<tr><td>Female, n (%)</td><td>21 (35%)</td><td>15 (36%)</td></tr>
<tr><td>Mean age, years (SD)</td><td>12.7 (3.6)</td><td>14.5 (2.4)</td></tr>
</table>
</td>
<td>US</td>
<td>60 participants were in the study.

HRQoL outcome measures were presented for 40 out of the 60 included participants (all paediatric patients, aged 10—18).</td>
<td>HRQoL reported for the patient population, all of which had NF1 PN.

HRQoL for specific adverse events are not reported.</td>
<td>HRQoL was assessed using the IPI form.

Caregivers completed the forms for all participants, and parallel self-report forms were completed by adolescents (ages 10-18) and adults >18.</td>
<td>Table 1. Patient HRQoL scores measured by IPI
<table>
<tr><th>Population (N=40)</th><th>Mean (range [SD])</th></tr>
<tr><td>Caregiver rating</td><td>68.7 (45.7—92.1 [12.7])</td></tr>
<tr><td>Adolescent self-report</td><td>68.4 (48.0—87.5 [11.2])</td></tr>
<tr><td>Moderate/severe disease, caregiver</td><td>64.2</td></tr>
<tr><td>Mild disease, caregiver</td><td>79.2</td></tr>
<tr><td>Moderate/severe disease, self-report</td><td>65.3</td></tr>
<tr><td>Mild disease, self-report</td><td>74.8</td></tr>
</table>
Abbreviations: HRQoL: health related quality of life; IPI: Impact of Pediatric Illness form; SD: standard deviation</td>
<td>Consistency with NICE reference case:
No generic, preference-based instruments were included, and thus no suitable data were available that could be used to generate utility values to inform the cost-effectiveness analysis.
The similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.</td>
</tr>
</table>

Source	Description of population and recruitment method			Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	Age range	6.3–18.8	10.6–18.8						**Relevance to the decision problem:** Patients included have NF1 PN and are a paediatric population, so are relevant to the decision problem. It is unclear whether the PN are inoperable, limiting relevance to the decision problem.
	Disease severity, moderate /severe *, n (%)	42 (70%)	28 (67%)						
	Disease visibility, mild*, n (%)	18 (30%)	14 (33%)						
	*Rated by the carer on a scale of mild, moderate, or severe **Abbreviations**: SD: standard deviation								

17.6 Appendix 6: Resource identification, measurement and valuation

The following information should be provided.

17.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

See the economic evidence search in Section 17.4.1.

17.6.2 The date on which the search was conducted.

See the economic evidence search in Section 17.4.2.

17.6.3 The date span of the search.

See the economic evidence search in Section 17.4.3.

17.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See the economic evidence search in Section 17.4.4.

17.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See the economic evidence search in Section 17.4.5.

17.6.6 The inclusion and exclusion criteria.

See Table D1 in Section 11.1.2.

17.6.7 The data abstraction strategy.

See the economic evidence search in Section 17.4.7.

17.6.8 Included and excluded study tables

A list of studies included in the cost and resource use stream of the SLR can be found in Table 72. A list of studies excluded in the cost and resource use stream of the SLR following full-text review can be found in Table 73, alongside reasoning for exclusion.

Table 72. List of studies included in the cost and resource use SLR

#	Study name	Citation
1	Rosser 2018	Rosser T. Substantial Pain and Reduced Quality of Life (QOL) in Adolescents and Young Adults (AYA) with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibromas (PNs) Enrolled in NF Consortium PN Clinical Trials. International Symposium on Pediatric Neuro-Oncology (ISPNO) 2018.
2	Widemann 2014 (NCT00021541)	Widemann BC, Dombi E, Gillespie A, et al. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro-Oncology 2014;16:707-718.
3	Wolters 2015	Wolters PL, Burns KM, Martin S, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. American Journal of Medical Genetics, Part A 2015;167:2103-2113.
4	Yang 2020	Yang X, Desai K, Agrawal N, et al. Treatment, resource use and costs among pediatric patients with neurofibromatosis type 1 and plexiform neurofibromas. Pediatric Health, Medicine and Therapeutics 2020;11:421-428.

Abbreviations: SLR: systematic literature review

Table 73. List of studies excluded in the cost and resource use SLR, following full-text review, alongside reasoning for exclusion

#	Citation	Reason for exclusion
1	Acarturk TO, Yigenoglu B, Pekedis O. Excision and "transcutaneous" lift in patients with neurofibromatosis of the fronto-temporo-orbital and auricular regions. Journal of Craniofacial Surgery 2009;20:771-4.	Irrelevant study design
2	Afridi SK, Leschziner GD, Ferner RE. Prevalence and clinical presentation of headache in a National Neurofibromatosis 1 Service and impact on quality of life. American Journal of Medical Genetics, Part A 2015;167:2282-2285.	Doesn't report CRU data
3	Algermissen B, Muller U, Katalinic D, et al. CO<inf>2</inf> laser treatment of neurofibromas of patients with neurofibromatosis type 1: Five years experience. Medical Laser Application 2001;16:265-274.	CRU data not in a PN population

#	Citation	Reason for exclusion
4	Avery RA, Hardy KK. Vision specific quality of life in children with optic pathway gliomas. Journal of Neuro-Oncology 2014;116:341-347.	Doesn't report CRU data
5	Bergqvist C, Servy A, Valeyrie-Allanore L, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet journal of rare diseases 2020;15:37.	Irrelevant study design
6	Bicudo NP, de Menezes Neto BF, da Silva de Avo LR, et al. Quality of Life in Adults with Neurofibromatosis 1 in Brazil. Journal of genetic counseling 2016;25:1063-1074.	Doesn't report CRU data
7	Bottesi G, Spoto A, Trevisson E, et al. Dysfunctional coping is related to impaired skin-related quality of life and psychological distress in patients with neurofibromatosis type 1 with major skin involvement. British Journal of Dermatology 2020;182:1449-1457.	Doesn't report CRU data
8	Brenaut E, Nizery-Guermeur C, Audebert-Bellanger S, et al. Clinical Characteristics of Pruritus in Neurofibromatosis 1. Acta Dermato-Venereologica 2016;96:398-9.	Doesn't report CRU data
9	Brunt LM, Lairmore TC, Doherty GM, et al. Adrenalectomy for familial pheochromocytoma in the laparoscopic era. Annals of Surgery 2002;235:713-721.	Irrelevant study design
10	Chamseddin BH, Hernandez L, Solorzano D, et al. Robust surgical approach for cutaneous neurofibroma in neurofibromatosis type 1. JCI Insight 2019;4 (11) (no pagination).	Doesn't report CRU data
11	Cipolletta S, Spina G, Spoto A. Psychosocial functioning, self-image, and quality of life in children and adolescents with neurofibromatosis type 1. Child: care, health and development 2018;44:260-268.	Doesn't report CRU data
12	Cohen JS, Levy HP, Sloan J, et al. Depression among adults with neurofibromatosis type 1: Prevalence and impact on quality of life. Clinical Genetics 2015;88:425-430.	Doesn't report CRU data
13	Copley-Merriman C, Yang X, Juniper M, et al. Pro85 Impact of Neurofibromatosis Type 1 and Plexiform Neurofibromas on Patient-Reported Health-Related Quality of Life. Value in Health 2020;23 (Supplement 1):S344.	Irrelevant study design
14	Cosyns M, Mortier G, Janssens S, et al. Voice-related quality of life in adults with neurofibromatosis type 1. Journal of Voice 2012;26:e57-e62.	Doesn't report CRU data
15	Coutinho V, Camara-Costa H, Kemlin I, et al. The Discrepancy between Performance-Based Measures and Questionnaires when Assessing Clinical Outcomes and Quality of Life in Pediatric Patients with Neurological Disorders. Applied neuropsychology 2017;Child. 6:255-261.	Doesn't report CRU data
16	Dakwar E, Smith WD, Malone KT, et al. Minimally invasive lateral extracavitary resection of foraminal neurofibromas. Journal of Clinical Neuroscience 2011;18:1510-2.	Doesn't report CRU data
17	Dolan KD, Yuh WT. Gadolinium-enhanced facial nerves: accompanying bilateral acoustic tumors in patient with neurofibromatosis. Annals of Otology, Rhinology & Laryngology 1989;98:747-8.	Irrelevant study design
18	Doser K, Andersen EW, Kenborg L, et al. Clinical characteristics and quality of life, depression, and anxiety in adults with	Doesn't report CRU data

#	Citation	Reason for exclusion
	neurofibromatosis type 1: A nationwide study. American Journal of Medical Genetics, Part A 2020;182:1704-1715.	
19	Draucker CB, Nutakki K, Varni JW, et al. The health-related quality of life of children, adolescents, and young adults with neurofibromatosis type 1 and their families: Analysis of narratives. Journal for specialists in pediatric nursing : JSPN 2017;22.	Doesn't report CRU data
20	Ehara Y, Koga M, Imafuku S, et al. Distribution of diffuse plexiform neurofibroma on the body surface in patients with neurofibromatosis 1. Journal of Dermatology 2020;47:190-192.	Doesn't report CRU data
21	Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. The Lancet Oncology 2019;20:1011-1022.	Doesn't report CRU data
22	Farmer JP, Khan S, Khan A, et al. Neurofibromatosis type 1 and the pediatric neurosurgeon: A 20-year institutional review. Pediatric Neurosurgery 2002;37:122-136.	CRU data not in a PN population
23	Ferner RE, Thomas M, Mercer G, et al. Evaluation of quality of life in adults with neurofibromatosis 1 (NF1) using the Impact of NF1 on Quality Of Life (INF1-QOL) questionnaire. Health and Quality of Life Outcomes 2017;15 (1) (no pagination).	Doesn't report CRU data
24	Fisher MJ, Shih CS, Rhodes SD, et al. Cabozantinib for neurofibromatosis type 1-related plexiform neurofibromas: a phase 2 trial. Nat Med 2021;27:165-173.	Doesn't report CRU data
25	Fjermestad KW, Nyhus L, Kanavin OJ, et al. Health Survey of Adults with Neurofibromatosis 1 Compared to Population Study Controls. Journal of genetic counseling 2018;27:1102-1110.	Doesn't report CRU data
26	Fjermestad KW. Health complaints and work experiences among adults with neurofibromatosis 1. Occupational medicine (Oxford, England) 2019;69:504-510.	Doesn't report CRU data
27	Fletcher AN, Schwend RM. The Ecuador Pediatric Spine Deformity Surgery Program: An SRS-GOP Site, 2008-2016. Spine Deformity 2019;7:220-227.	Irrelevant study design
28	Flood TF, Stence NV, Maloney JA, et al. Pediatric brain: Repeated exposure to linear gadolinium-based contrast material is associated with increased signal intensity at unenhanced T1-weighted MR imaging. Radiology 2017;282:222-228.	Irrelevant population
29	Freedman I, Koo A, Yeagle E, et al. Does neurofibromatosis 1 status impact outcomes for pediatric/young adults undergoing spinal fusion? Surgical Neurology International 2020;11 (60) (no pagination).	CRU data not in a PN population
30	Furlong W, Barr RD, Feeny D, et al. Patient-focused measures of functional health status and health-related quality of life in pediatric orthopedics: A case study in measurement selection. Health and Quality of Life Outcomes 2005;3 (no pagination).	Irrelevant study design
31	Gilboa Y, Rosenblum S, Fattal-Valevski A, et al. Application of the International Classification of Functioning, Disability and Health in children with neurofibromatosis type 1: a review. Developmental Medicine & Child Neurology 2010;52:612-9.	Irrelevant study design

#	Citation	Reason for exclusion
32	Giudice G, Favia G, Tempesta A, et al. Confocal microscopy predicts the risk of recurrence and malignant transformation of mucocutaneous neurofibromas in NF-1: An observational study. Dermatology Research and Practice 2018;2018 (no pagination).	Doesn't report CRU data
33	Goetsch Weisman A, Haws T, Lee J, et al. Transition Readiness Assessment in Adolescents and Young Adults with Neurofibromatosis Type 1 (NF1). Comprehensive child and adolescent nursing 2020:1-17.	Doesn't report CRU data
34	Graf A, Landolt MA, Mori AC, et al. Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1. Journal of Pediatrics 2006;149:348-353.	Doesn't report CRU data
35	Griffiths S, Thompson P, Frayling I, et al. Molecular diagnosis of neurofibromatosis type 1: 2 Years experience. Familial Cancer 2007;6:21-34.	Doesn't report CRU data
36	Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. New England Journal of Medicine 2020;382:1430-1442.	Doesn't report CRU data
37	Guiraud M, Bouroubi A, Beauchamp R, et al. Cutaneous neurofibromas: Patients' medical burden, current management and therapeutic expectations: Results from an online European patient community survey. Orphanet Journal of Rare Diseases 2019;14 (1) (no pagination).	CRU data not in a PN population
38	Hamoy-Jimenez G, Kim R, Suppiah S, et al. Quality of life in patients with neurofibromatosis type 1 and 2 in Canada. Neuro-oncology Advances 2020;2:i141-i149.	Doesn't report CRU data
39	Hivelin M, Wolkenstein P, Lepage C, et al. Facial aesthetic unit remodeling procedure for neurofibromatosis type 1 hemifacial hypertrophy: report on 33 consecutive adult patients. Plastic & Reconstructive Surgery 2010;125:1197-207.	CRU data not in a PN population
40	Holzapfel J, Kandels D, Schmidt R, et al. Favorable prognosis in pediatric brainstem low-grade glioma: Report from the German SIOP-LGG 2004 cohort. International Journal of Cancer 2020;146:3385-3396.	Doesn't report CRU data
41	Iannicelli E, Rossi G, Almberger M, et al. Integrated imaging in peripheral nerve lesions in type 1 neurofibromatosis. La Radiologia medica 2002;103:332-343.	CRU data not in a PN population
42	Imperato A CG, Meccariello G. Optic pathway gliomas of the pediatric age: impact of neurosurgery on quality of life. Child's Nervous System 2018;34:1022.	Doesn't report CRU data
43	Kalakoti P, Missios S, Menger R, et al. Association of risk factors with unfavorable outcomes after resection of adult benign intradural spine tumors and the effect of hospital volume on outcomes: an analysis of 18, 297 patients across 774 US hospitals using the National Inpatient Sample (2002-2011). Neurosurgical focus 2015;39:E4.	Doesn't report CRU data
44	Kodra Y, Giustini S, Divona L, et al. Health-related quality of life in patients with neurofibromatosis type 1: A survey of 129 Italian patients. Dermatology 2009;218:215-220.	Doesn't report CRU data

#	Citation	Reason for exclusion
45	Kondyli M, Larouche V, Saint-Martin C, et al. Trametinib for progressive pediatric low-grade gliomas. Journal of Neuro-Oncology 2018;140:435-444.	Irrelevant study design
46	Kongkriangkai AM, King C, Martin LJ, et al. Substantial pain burden in frequency, intensity, interference and chronicity among children and adults with neurofibromatosis Type 1. American Journal of Medical Genetics, Part A 2019;179:602-607.	Doesn't report CRU data
47	Krab LC, Oostenbrink R, de Goede-Bolder A, et al. Health-Related Quality of Life in Children with Neurofibromatosis Type 1: Contribution of Demographic Factors, Disease-Related Factors, and Behavior. Journal of Pediatrics 2009;154:420-425.Irrelevant study design.	Doesn't report CRU data
48	Kurucan E, Bernstein DN, Thirukumaran C, et al. National Trends in Spinal Fusion Surgery for Neurofibromatosis. Spine Deformity 2018;6:712-718.	CRU data not in a PN population
49	Kuwahara M, Yurugi S, Iioka H, et al. Problems on resecting the neurofibromatosis type 1 from experiences of 17 patients. [Japanese]. Skin Research 2004;3:591-596.	Doesn't report CRU data
50	Lai JS, Jensen SE, Charrow J, et al. Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders Measurement System to Evaluate Quality of Life for Children and Adolescents with Neurofibromatosis Type 1 Associated Plexiform Neurofibroma. Journal of Pediatrics 2019;206:190-196.	CRU data not in a PN population
51	Lantieri L, Grimbert P, Ortonne N, et al. Face transplant: long-term follow-up and results of a prospective open study. The Lancet 2016;388:1398-1407.	Irrelevant study design
52	Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II weekly vinblastine for chemotherapy-naive children with progressive low-grade glioma: A Canadian pediatric brain tumor consortium study. Journal of Clinical Oncology 2016;34:3537-3543.	Doesn't report CRU data
53	Lundar T, Due-Tonnessen BJ, Egge A, et al. Neurosurgical treatment of pediatric low-grade midbrain tumors: a single consecutive institutional series of 15 patients. Journal of neurosurgery 2014;Pediatrics. 14:598-603.	Irrelevant study design
54	Lyu Q, Zhou C, Song Y, et al. Does spinal deformity correction of non-dystrophic scoliosis in neurofibromatosis type I with one-stage posterior pedicle screw technique produce outcomes similar to adolescent idiopathic scoliosis? Spine Journal 2017;17:1850-1858.	CRU data not in a PN population
55	Maloney E, Stanescu AL, Perez FA, et al. Surveillance magnetic resonance imaging for isolated optic pathway gliomas: is gadolinium necessary? Pediatric Radiology 2018;48:1472-1484.	CRU data not in a PN population
56	Marsault P, Ducassou S, Menut F, et al. Diagnostic performance of an unenhanced MRI exam for tumor follow-up of the optic pathway gliomas in children. Neuroradiology 2019;61:711-720.	CRU data not in a PN population
57	Marsault P, Menut F, Bessou P, et al. Optic pathway gliomas: MRI follow-up including imaging with gadolinium-based contrast agent: Accuracy of non-enhancement sequences for diagnosis of progression. Pediatric Radiology 2019;49 (Supplement 2):S311.	Doesn't report CRU data

#	Citation	Reason for exclusion
58	Mauger D, Zeller J, Revuz J, et al. Psychological impact of neurofibromatosis type 1: Analysis of interviews with 12 patients to evaluate quality of life. [French]. Annales de Dermatologie et de Venereologie 1999;126:619-620.	Irrelevant study design
59	Merker VL, Bredella MA, Cai W, et al. Relationship between whole-body tumor burden, clinical phenotype, and quality of life in patients with neurofibromatosis. American Journal of Medical Genetics, Part A 2014;164:1431-1437.	Doesn't report CRU data
60	Metalwala Z, Okunseri C, Fletcher S, et al. Orthognathic Surgical Outcomes in Patients With and Without Craniofacial Anomalies. Journal of Oral and Maxillofacial Surgery 2018;76:436.Irrelevant study design-436.e8.	Irrelevant population
61	Miraglia E, Calvieri S, Giustini S. Pruritus in neurofibromatosis type 1. Giornale Italiano di Dermatologia e Venereologia 2018;153:120-122.	Doesn't report CRU data
62	Morandell E, Salandin M, Mantovan F. [Experiences of patients with neurofibromatosis type 1 and their families or caregivers]. Kinderkrankenschwester 2013;32:102-5.	Irrelevant study design
63	Muram TM, Stevenson DA, Watts-Justice S, et al. A cost savings approach to SPRED1 mutational analysis in individuals at risk for neurofibromatosis type 1. American Journal of Medical Genetics, Part A 2013;161:467-472.	Doesn't report CRU data
64	Newman WC, Berry-Candelario J, Villavieja J, et al. Improvement in Quality of Life Following Surgical Resection of Benign Intradural Extramedullary Tumors: A Prospective Evaluation of Patient-Reported Outcomes. Neurosurgery 2021.	Irrelevant population
65	Nutakki K, Hingtgen CM, Monahan P, et al. Development of the adult PedsQL TM neurofibromatosis type 1 module: initial feasibility, reliability and validity. Health & Quality of Life Outcomes 2013;11:21.	Doesn't report CRU data
66	Nutakki K, Hingtgen CM, Monahan P, et al. Development of the Adult PedsQLTM Neurofibromatosis Type 1 Module: Initial Feasibility, Reliability and Validity. Health and Quality of Life Outcomes 2013;11 (1) (no pagination).	Doesn't report CRU data
67	Nutakki K, Varni JW, Steinbrenner S, et al. Development of the pediatric quality of life inventory neurofibromatosis type 1 module items for children, adolescents and young adults: qualitative methods. Journal of Neuro-Oncology 2017;132:135-143.	Doesn't report CRU data
68	Nutakki K, Varni JW, Swigonski NL. PedsQL Neurofibromatosis Type 1 Module for children, adolescents and young adults: feasibility, reliability, and validity. Journal of Neuro-Oncology 2018;137:337-347.	Doesn't report CRU data
69	Oostenbrink R, Spong K, de Goede-Bolder A, et al. Parental Reports of Health-Related Quality Of Life in Young Children with Neurofibromatosis Type 1: Influence of Condition Specific Determinants. Journal of Pediatrics 2007;151:182-186.Irrelevant population.	Doesn't report CRU data
70	Pacheco-Cuellar G, Castaneda-Saldana I, Valdez-Andrade J, et al. P-294 Incorporating genetic counseling service into the gastrointestinal tumor board: Experience, obstacles, and	Irrelevant study design

#	Citation	Reason for exclusion
	opportunities in a Mexican center. Annals of Oncology 2020;31 (Supplement 3):S185-S186.	
71	Page PZ, Page GP, Ecosse E, et al. Impact of neurofibromatosis 1 on quality of life: A cross-sectional study of 176 American cases. American Journal of Medical Genetics, Part A 2006;140:1893-1898.	Doesn't report CRU data
72	Payne JM, Barton B, Ullrich NJ, et al. Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1. Neurology 2016;87:2575-2584.	Doesn't report CRU data
73	Reichman M, Riklin E, Macklin E, et al. Virtual mind-body treatment for adolescents with neurofibromatosis: Study protocol for a single-blind randomized controlled trial. Contemporary Clinical Trials 2020;95 (no pagination).	Doesn't report CRU data
74	Ren JY, Gu YH, Wei CJ, et al. Evaluation and Factors of Quality of Life Among Patients With Neurofibromatosis Type 1-Associated Craniofacial Plexiform Neurofibromas. The Journal of craniofacial surgery 2020;31:347-350.	Irrelevant population
75	Ruegg EM, Hivelin M, Hemery F, et al. Face transplantation program in France: a cost analysis of five patients. Transplantation 2012;93:1166-72.	Doesn't report CRU data
76	Saltik S, Basgul SS. [Quality of life in children with neurofibromatosis type 1, based on their mothers' reports]. Turk Psikiyatri Dergisi 2013;24:25-34.	Irrelevant study design
77	Sanagoo A, Jouybari L, Koohi F, et al. Evaluation of QoL in neurofibromatosis patients: A systematic review and meta-analysis study. BMC Neurology 2019;19 (1) (no pagination).	Doesn't report CRU data
78	Schooler GR, Davis JT, Daldrup-Link HE, et al. Current utilization and procedural practices in pediatric whole-body MRI. Pediatric Radiology 2018;48:1101-1107.	Irrelevant study design
79	Shah M, Mavers M, Bree A, et al. Quality of life and depression assessment in nevoid basal cell carcinoma syndrome. International Journal of Dermatology 2011;50:268-76.	Doesn't report CRU data
80	Shin DW, Sohn MJ, Kim HS, et al. Clinical analysis of spinal stereotactic radiosurgery in the treatment of neurogenic tumors. Journal of neurosurgery 2015;Spine. 23:429-437.	Irrelevant population
81	Soghi I, Saeedi S, Sanagoo A, et al. Quality of life in a group of Iranian patients with neurofibromatosis type 1 with cutaneous expressions. [Persian]. Journal of Mazandaran University of Medical Sciences 2018;28:95-103.	Irrelevant population
82	Soulier G, van Leeuwen BM, Putter H, et al. Quality of Life in 807 Patients with Vestibular Schwannoma: Comparing Treatment Modalities. Otolaryngology - Head and Neck Surgery (United States) 2017;157:92-98.	Doesn't report CRU data
83	Spuijbroek AT, Oostenbrink R, Landgraf JM, et al. Health-related quality of life in preschool children in five health conditions. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:779-786.	Irrelevant population
84	Tora MS, Xenos D, Texakalidis P, et al. Treatment of neurofibromatosis 1-associated malignant peripheral nerve sheath	Doesn't report CRU data

#	Citation	Reason for exclusion
	tumors: a systematic review. Neurosurgical Review 2020;43:1039-1046.	
85	Tsang E, Birch P, Friedman JM. Valuing gene testing in children with possible neurofibromatosis 1. Clinical Genetics 2012;82:591-593.	Irrelevant study design
86	Turkson L, Mamuszka H, Grimshaw K, et al. Abstract 5288: MPNST treatment and diagnosis in NF1: A health economic model. Cancer Research 2018;78:5288.	Doesn't report CRU data
87	Van Der Vaart T, Rietman AB, Plasschaert E, et al. Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology 2016;86:154-160.	Doesn't report CRU data
88	Vardarinos A, Zafeiriou DI, Vargiami E, et al. Parental reports of health-related quality of life in greek children with neurofibromatosis type 1. Journal of Pediatrics 2009;155:453.	Doesn't report CRU data
89	Varni JW, Nutakki K, Swigonski NL. Cognitive functioning and pain interference mediate pain predictive effects on health-related quality of life in pediatric patients with Neurofibromatosis Type 1. European Journal of Paediatric Neurology. 2020.	Doesn't report CRU data
90	Varni JW, Nutakki K, Swigonski NL. Pain, skin sensations symptoms, and cognitive functioning predictors of health-related quality of life in pediatric patients with Neurofibromatosis Type 1. Quality of Life Research 2019;28:1047-1052.	Doesn't report CRU data
91	Varni JW, Nutakki K, Swigonski NL. Speech difficulties and patient health communication mediating effects on worry and health-related quality of life in children, adolescents, and young adults with Neurofibromatosis Type 1. American Journal of Medical Genetics, Part A 2019;179:1476-1482.	Doesn't report CRU data
92	Vassallo G, Mughal Z, Robinson L, et al. Perceived fatigue in children and young adults with neurofibromatosis type 1. Journal of Paediatrics & Child Health 2020;56:878-883.	Doesn't report CRU data
93	Vranceanu AM, Merker VL, Park E, et al. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: A systematic review of the literature. Journal of Neuro-Oncology 2013;114:257-262.	Doesn't report CRU data
94	Vranceanu AM, Merker VL, Park ER, et al. Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature. Journal of Neuro-Oncology 2015;122:219-28.	Irrelevant study design
95	Wang J, Liu C, Wang C, et al. Early and Midterm Outcomes of Surgical Correction for Severe Dystrophic Cervical Kyphosis in Patients with Neurofibromatosis Type 1: A Retrospective Multicenter Study. World Neurosurgery 2019;127:Irrelevant study design190-Irrelevant study design200.	Irrelevant study design
96	Weiss B, Widemann BC, Wolters P, et al. Sirolimus for non-progressive NF1-associated plexiform neurofibromas: An NF clinical trials consortium phase II study. Pediatric Blood and Cancer 2014;61:982-986.	Doesn't report CRU data
97	Wiener L, Battles H, Bedoya SZ, et al. Identifying Symptoms of Distress in Youth Living with Neurofibromatosis Type 1 (NF1). Journal of Genetic Counseling 2018;27:115-123.	Doesn't report CRU data

#	Citation	Reason for exclusion
98	Wolkenstein P, Durand-Zaleski I, Moreno JC, et al. Cost evaluation of the medical management of neurofibromatosis 1: A prospective study on 201 patients. British Journal of Dermatology 2000;142:1166-1170.	Doesn't report CRU data
99	Wolkenstein P, Loundou A, Barrau K, et al. Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. Journal of the American Academy of Dermatology 2007;56:621-3.	CRU data not in a PN population
100	Wolkenstein P, Rodriguez D, Ferkal S, et al. Impact of neurofibromatosis 1 upon quality of life in childhood: A cross-sectional study of 79 cases. British Journal of Dermatology 2009;160:844-848.	Doesn't report CRU data
101	Wolkenstein P, Zeller J, Revuz J, et al. Quality-of-life impairment in neurofibromatosis type 1: A cross-sectional study of 128 cases. Archives of Dermatology 2001;137:1421-1425.	Doesn't report CRU data
102	Wolsey DH, Larson SA, Creel D, et al. Can Screening for Optic Nerve Gliomas in Patients With Neurofibromatosis Type I Be Performed With Visual-Evoked Potential Testing? Journal of AAPOS 2006;10:307-311.	Doesn't report CRU data
103	Yamauchi T, Suka M, Nishigori C, et al. Evaluation of neurofibromatosis type 1 progression using a nationwide registry of patients who submitted claims for medical expense subsidies in Japan between 2008 and 2012. Orphanet Journal of Rare Diseases 2019;14 (1) (no pagination).	Doesn't report CRU data
104	Yifei G, Xiaolong S, Yang L, et al. Clinical outcomes of anterior correction and reconstruction for neurofibromatosis-associated severe cervical kyphotic deformity. International Orthopaedics 2019;43:639-646.	Doesn't report CRU data
105	Zehou O, Ferkal S, Brugieres P, et al. Absence of Efficacy of Everolimus in Neurofibromatosis 1-Related Plexiform Neurofibromas: Results from a Phase 2a Trial. Journal of Investigative Dermatology 2019;139:718-720.	Doesn't report CRU data

Abbreviations: CRU: cost and resource use; SLR: systematic literature review.

17.6.9 Cost and resource use study extractions

Table 74. Summary of cost and resource use studies included in the economic SLR

<table>
<tr><th>Source</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td>Rosser 2018[155]</td><td>Objective:
To examine patient-reported outcomes collected prior to treatment in PN clinical trials. Patient medication use also reported.

Patient population
NF1 patients with symptomatic and inoperable PN, aged >16 years.

Population characteristics
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Males (n)</td><td>20</td></tr>
<tr><td>Females (n)</td><td>18</td></tr>
<tr><td>Median age (years)</td><td>23</td></tr>
<tr><td>Age range (years)</td><td>16–39</td></tr>
<tr><td>Tumour visibility, mild (%)*</td><td>40</td></tr>
<tr><td>Tumour visibility, moderate (%)*</td><td>47</td></tr>
<tr><td>Tumour visibility, severe (%)*</td><td>13</td></tr>
<tr><td>NF1 symptoms, mild (%)</td><td>26</td></tr>
</table></td><td>US

Cost year not reported.</td><td>Trial methodology not reported.

Patients enrolled in the trials completed a background information form at baseline.

No additional data sources.</td><td>Of 38 patients, 42% took pain medication regularly and 23% took prescription medication.</td><td>Applicability to clinical practice in England:
The study took place in the US; the similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.

Suitability of cost and resource use data to the cost-effectiveness analysis:
Patients included were NF1 patients</td></tr>
</table>

Source	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis
	<table><tr><td>NF1 symptoms, moderate (%)*</td><td>50</td></tr><tr><td>NF1 symptoms, severe (%)*</td><td>24</td></tr><tr><td>Mean (SD) NRS-11 score</td><td>5.3 (3.0)</td></tr><tr><td>Mild tumour pain (%)</td><td>21</td></tr><tr><td>Moderate tumour pain (%)</td><td>29</td></tr><tr><td>Severe tumour pain (%)</td><td>40</td></tr></table> *Patients rated own disease visibility and symptom severity on a scale of mild, moderate, or severe **Abbreviations**: NF1: Neurofibromatosis type 1; NRS-11: Numeric Pain Rating Scale-11; SD: standard deviation. Recruitment This patient population are from two clinical trials (NCT02101736 and NCT02096471) before receiving treatment. Details of recruitment are not reported.				with inoperable and symptomatic PN, so is aligned to the decision problem; however, the study included adults as well as children, limiting the applicability to the decision problem.
Widemann 2014 (NCT00021541)[41]	Phase II randomised, flexible crossover, double-blinded, placebo-controlled trial. Objective	US Cost year not reported.	Participants' prior medical treatment for their PN was recorded at	Participants' prior treatments for PN <table><tr><th>Treatment</th><th>Participants (n=60)</th></tr><tr><td>Any</td><td>12</td></tr><tr><td>Methotrexate/vinblastine</td><td>6</td></tr><tr><td>Pirfenidone</td><td>3</td></tr></table>	**Applicability to clinical practice in England:** The study took place in the US; the similarities between

Source	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis
	To investigate the efficacy, safety and HRQoL in the treatment of children and young adults with NF1 and PN with tipifarnib. Patients Children and young adults ≥3 and ≤25 years with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity, meeting the eligibility criteria were included. Patients who underwent prior surgery for their progressive PN were eligible provided the residual tumour was measurable. Key eligibility criteria Measurable, progressive PN (≥3 cm in one dimension; ≥20% increase in volume, or ≥13% increase in 2D/≥ 6% increase in 1D measurement over last two consecutive MRI scans); recovered from prior therapy to grade ≤1 organ function toxicity; ECOG PS 0–2; ANC ≥1,500/μL; Hb ≥9.0 g/dL; platelet count		baseline for 60 participants. No additional data sources were given.	Cis retinoic acid 1 Peginterferon alfa 2B 1 Thalidomide 1 **Abbreviations**: PN: plexiform neurofibroma.	the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England. **Suitability of cost and resource use data to the cost-effectiveness analysis:** The patient population includes NF1 patients with inoperable PN. However, it is unclear whether the PN were symptomatic, limiting applicability to the decision problem. In addition, the population is a

Source	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis
	≥150,000/μL; ALT ≤2xULN; age-adjusted normal serum creatinine. Population characteristics				mix of paediatric patients and young adults, limiting applicability.

Source	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis

Characteristic	Placebo	Tipifarnib
Median age (years)	8.2	9.7
Age range (years)	3–17	3–21.5
Male (n)	14	21
Female (n)	15	10
IPI Scale mean score	3.70	3.69
IPI emotional functioning subscale mean score	3.63	3.37
ECOG PS		
0	24	21
1	4	9
2	1	1
PNs	52	44
Target PNs*	31	32
Volume (mL)		
Median**	316	572
Range	39.6–4,896	20.5–5,573

*PN chosen for volumetric MRI analysis to determine time to progression.
**PN volume larger in tipifarnib group compared with placebo (p=0.09).
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance

<table>
<tr><th>Source</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td>Status; IPI: International Prognostic Index; PN: plexiform neurofibroma.

<u>Recruitment</u>
Patients were recruited from ten participating sites, enrolling seven total patients.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Wolters 2015[19]</td><td>Analysis of patients enrolled on a natural history protocol at NCI.

<u>Objective</u>
To investigate the impact of pain in youth with NF1 and PN and its relationship to disease factors, social-emotional functioning, and QoL within a biopsychosocial framework.

<u>Patients</u>
Patients included in the study were children and adolescents six to 18 years of age with NF1 PN.

Eligibility criteria included diagnosis of NF1 according to the NIH Consensus Conference criteria or a confirmed NF1 germline mutation with analysis</td><td>US

Cost year not reported.</td><td>The proportion of patients taking pain medication, and the medication type were reported by parents at the start of the study.</td><td><u>The proportion of patients taking pain medications (n=60)</u>
<table><tr><th>Type of pain medication</th><th>Number of patients</th></tr><tr><td>No regular pain medication</td><td>40</td></tr><tr><td>OTC only (acetaminophen, ibuprofen)</td><td>2</td></tr><tr><td>Prescription (with/without OTC medication)</td><td>18</td></tr><tr><td>Opioids</td><td></td></tr><tr><td>Morphine</td><td>1</td></tr><tr><td>Tylenol with codeine</td><td>5</td></tr><tr><td>Vicodin/hydrocodone</td><td>1</td></tr><tr><td>Anticonvulsants</td><td></td></tr><tr><td>Neurontin</td><td>6</td></tr><tr><td>Gabapentin</td><td>2</td></tr><tr><td>Pregabalin</td><td>1</td></tr><tr><td>Tegretol</td><td>1</td></tr></table></td><td>Applicability to clinical practice in England:
The study took place in the US; the similarities between the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.

Suitability of cost and resource use data to the cost-</td></tr>
</table>

<table>
<tr><th>Source</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td>performed in a CLIA-certified laboratory.

Population characteristics
<table><tr><th>Characteristic</th><th>Value</th></tr><tr><td>Female, n (%)</td><td>21 (35%)</td></tr><tr><td>Mean age, years (SD)</td><td>12.7 (3.6)</td></tr><tr><td>Age range</td><td>6.3–18.8</td></tr><tr><td>Disease severity, moderate/severe *, n (%)</td><td>42 (70%)</td></tr><tr><td>Disease visibility, mild*, n (%)</td><td>18 (30%)</td></tr></table>*Rated by the carer on a scale of mild, moderate, or severe.
Abbreviations: SD: standard deviation.

Recruitment
Patients were enrolled from a natural history protocol study at the NCI.</td><td></td><td></td><td><table><tr><td>Topiramate</td><td>1</td></tr><tr><td>Antidepressants</td><td></td></tr><tr><td>Amitriptyline</td><td>4</td></tr><tr><td>Rizatriptan</td><td>1</td></tr><tr><td>Zolmitriptan</td><td>1</td></tr><tr><td>Topical/local anaesthetics</td><td></td></tr><tr><td>Lidocaine patch</td><td>3</td></tr></table>**Abbreviations**: OTC: over the counter.</td><td>**effectiveness analysis:**
Patients included have NF1 PN and are a paediatric population, so are relevant to the decision problem. It is unclear whether the PN are inoperable, limiting relevance to the decision problem.</td></tr>
<tr><td>**Yang 2020[168]**</td><td>Objective
To describe the real-world demographics and clinical characteristics, treatment patterns, healthcare resource utilisation, and</td><td>US

The cost data were collected from</td><td>Patient data were collected from MarketScan® CCAE database.</td><td>All-cause resource use during the follow-up period among paediatric patients diagnosed with NF1 and PN (n=301)
<table><tr><th>Resource</th><th>N (%)</th><th>Mean (SD)*</th><th>Median (range)</th><th>Mean (SD) PPPY*</th></tr></table></td><td>**Applicability to clinical practice in England:**
The study was set in the US; the similarities between</td></tr>
</table>

<table>
<tr><th>Source</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr>
<td></td>
<td>costs among paediatric patients diagnosed with NF1 and PN in the US.

Patients
Patients included in this study were diagnosed with both NF1 and PN, aged ≤18 on the index date, and continuously enrolled for ≥12 months before the index date. Continuous enrolment was defined as no lapse in insurance coverage longer than 45 days.

Population characteristics[a]
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Female, n (%)</td><td>153 (50.8)</td></tr>
<tr><td>Male, n (%)</td><td>148 (49.2)</td></tr>
<tr><td>Mean age (years) (SD)</td><td>11.7 (4.6)</td></tr>
</table>
[a]Values are captured at index date or date nearest to the index date in the baseline period (if there is no record at index date).
Abbreviations: SD: standard deviation.

Recruitment
Patient claims data were collected from the MarketScan® CCAE database.</td>
<td>October 2014 to March 2018. All costs were adjusted to 2018 US dollars based on the medical care component of the Consumer Price Index.</td>
<td>Patient data were collected from the baseline, index and follow-up periods. The index date was the date of first diagnosis of NF1 or PN, whichever occurred later, on or after October 1, 2015.

The baseline period was defined as the 12-month period before the index date. The follow-up period varied in length,</td>
<td>
<table>
<tr><td>Inpatient visits</td><td>39 (13.0)</td><td>1.8 (1.5)</td><td>1.0 (1.0–9.0)</td><td>1.2 (1.5)</td></tr>
<tr><td>ER visits</td><td>76 (25.2)</td><td>2.1 (2.1)</td><td>1.0 (1.0–11.0)</td><td>1.3 (1.2)</td></tr>
<tr><td>Outpatient visits</td><td>300 (99.7)</td><td>24.8 (27.1)</td><td>15.0 (1.0–183.0)</td><td>18.2 (15.4)</td></tr>
<tr><td>Pharmacy visits</td><td>244 (81.1)</td><td>14.5 (19.1)</td><td>8.5 (1.0–140.0)</td><td>9.8 (10.6)</td></tr>
<tr><td>Other visits</td><td>153 (50.8)</td><td>6.2 (14.6)</td><td>2.0 (1.0–141.0)</td><td>4.1 (8.7)</td></tr>
</table>
*Mean value among patients with each type of HCRU. Patients without HCRU were not counted in the denominator.
Abbreviations: ER: emergency room; HCRU: health cost and resource use; PPPY: per patient per year; QoL: quality of life; SD: standard deviation.

Imaging services and treatment patterns during the follow-up period among paediatric patients diagnosed with NF1 and PN
<table>
<tr><th>Resource</th><th>N (%)</th></tr>
<tr><td colspan="2">Imaging services</td></tr>
<tr><td>Overall</td><td>213 (70.8)</td></tr>
<tr><td>MRI</td><td>208 (69.1)</td></tr>
</table>
</td>
<td>the NF1 PN patient population and current clinical management of NF1 PN patients in the US and UK mean the study is anticipated to be applicable to clinical practice in England.

Suitability of cost and resource use data to the cost-effectiveness analysis:
The patient population NF1 patients with inoperable PN. However, it is unclear whether the PN were symptomatic or inoperable, limiting applicability to the decision problem.</td>
</tr>
</table>

			spanning from the index date to the end of the study period or the end of continuous enrolment in the health plan, whichever occurred first. All-cause healthcare resource utilization included medical costs (inpatient, outpatient, ER and other encounters) and pharmacy costs. Treatments were broadly classified as surgery for PN, pain medication, chemotherapy, radiotherapy,	<table><tr><td>CT</td><td>42 (14.0)</td></tr><tr><td>PET</td><td>12 (4.0)</td></tr><tr><td colspan="2">Treatments</td></tr><tr><td>PN surgery</td><td>15 (5.0)</td></tr><tr><td>Pain treatments</td><td>133 (44.2)</td></tr><tr><td>Corticosteroids</td><td>60 (19.9)</td></tr><tr><td>Analgesics/NSAIDs</td><td>48 (16.0)</td></tr><tr><td>Opioids, opioid-like agents, and combination opioid/analgesics</td><td>48 (16.0)</td></tr><tr><td>Anticonvulsants</td><td>44 (14.6)</td></tr><tr><td>SSRIs</td><td>18 (6.0)</td></tr><tr><td>Other antidepressants</td><td>9 (3.0)</td></tr><tr><td>Tricyclic antidepressants</td><td>5 (1.7)</td></tr><tr><td>Topical products</td><td>3 (1.0)</td></tr><tr><td>Muscle relaxants</td><td>2 (0.7)</td></tr><tr><td>Chemotherapy</td><td>72 (23.9)</td></tr><tr><td>Dexamethasone[a,b]</td><td>50 (16.6)</td></tr><tr><td>Chemotherapy[c]</td><td>12 (4.0)</td></tr><tr><td>Carboplatin[a]</td><td>7 (2.3)</td></tr><tr><td>Methotrexate[a]</td><td>7 (2.3)</td></tr><tr><td>Tretinoin[a,b]</td><td>6 (2.0)</td></tr><tr><td>Radiotherapy</td><td>4 (1.3)</td></tr><tr><td>Targeted therapy</td><td>3 (1.0)</td></tr><tr><td>Trametinib dimethyl sulfoxide</td><td>2 (0.7)</td></tr><tr><td>Imatinib mesylate</td><td>1 (0.3)</td></tr></table>[a]Patients who have taken multiple medications from the list were counted more than once. [b]Dexamethasone and tretinoin may be used as non-chemotherapies in conditions other than cancers. [c]Identified as ‘chemotherapy’ in the procedure code.	

<table>
<tr><th>Source</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td></td><td></td><td>and targeted therapies. Claims for imaging services (CT, MRI and PET) were identified by the Healthcare Common Procedure Coding System and ICD PROC codes.

Healthcare costs PPPY were calculated as the total cost divided by the total number of days of enrolment in years, where costs were weighted by</td><td>Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging; NSAIDs: nonsteroidal anti-inflammatory drugs; PET: positron emission imagine; PN: plexiform neurofibroma; SSRI: selective serotonin reuptake inhibitor.

All-cause costs among paediatric patients diagnosed with NF1 and PN during the follow-up period.
<table><tr><th>Costs</th><th>Mean (SD) costs, PPPY</th><th>Median (LQ, UQ) costs, PPPY</th></tr><tr><td>Overall costs (Medical + Pharmacy)</td><td>$38,292.34 (80,556.01)</td><td>$16,036.71 (6,933.49, 40,137.84)</td></tr><tr><td>Total medical costs</td><td>$33,049.28 (75,908.36)</td><td>$14,827.64 (5,764.99, 35,805.89)</td></tr><tr><td>Inpatient costs</td><td>$9,323.42 (54,907.72)</td><td>$0.00 (-)</td></tr><tr><td>ER costs</td><td>$560.55 (2,059.20)</td><td>$0.00 (0.00, 383.37)</td></tr><tr><td>Outpatient costs</td><td>$22,297.38 (34,199.45)</td><td>$13,650.30 (5,164.36, 25,989.13)</td></tr><tr><td>Other costs</td><td>$867.93 (3,016.27)</td><td>$12.30 (0.00, 415.06)</td></tr></table></td><td></td></tr>
</table>

Source	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis
			each patient's length of follow-up to avoid overestimation and annualised for patients observed <1 year.	Pharmacy costs: $5,243.06 (23,319.18); $321.21 (28.87, 1,607.06) **Abbreviations**: ER: emergency room; LQ: lower quartile; PPPY: per patient per year; SD: standard deviation; UQ: upper quartile.	

Abbreviations: ALT: alanine transferase; ANC: absolute neutrophil count; CCAE: Commercial Claims and Encounters; CRU: cost and resource use; CT: computed tomography; CLIA: Clinical Laboratory Improvement Amendments; ECOG: Eastern Cooperative Oncology Group; ER: emergency room; Hb: haemoglobin; HRQoL: health related quality of life; ICD PROC, International Classification of Diseases Procedure Coding System; IPI: International Prognostic Index; LQ: lower quartile; MRI: magnetic resonance imagine; NCI: National Cancer Institute; NF1: neurofibromatosis 1; NHS: National Health Service; NR: not reported; NRS-11: 11-Item Numerical Rating Scale; NSAIDs: nonsteroidal anti-inflammatory drugs; OTC: over the counter; PET: positron emission imagine; PNs: plexiform neurofibromas; PPPY: per patient per year; QoL: quality of life; SD: standard deviation; SLR: systematic literature review; SSRI: selective serotonin reuptake inhibitor; ULN: upper limit of normal; US: United States of America; UQ: upper quartile.

17.7 Appendix 7: Additional information

17.7.1 Tipifarnib study 01-C-0222 supplementary information

Clinical baseline characteristics of patients in the two arms in phase A of the tipifarnib study 01-C-0222 are presented in Table 75.

Table 75. Clinical characteristics of 60 eligible participants in phase A of the tipifarnib study

	Total	Placebo	Tipifarnib
Participants enrolled (n)	60	29	31
Sex (M:F)	35:25	14:15	21:10[a]
Age in years: Median (range)	8.5 (3–21.5)	2 (3–17.7)	9.7 (3–21.5)
ECOG performance score			
0	45	24	21
1	13	4	9
2	2	1	1
PN characteristics			
Number of PN observed	96	52	44
Number of target PN[b]	63	31	32
Volume (mL): Median (range)	364 (20.5-5573)	316 (39.6-4896)	572 (20.5-5573)[c]
Location: target/observed			
Neck & chest	15/20	9/12	6/8
Trunk & extremity	12/18	3/7	9/11
Pelvis	10/12	6/7	4/5
Face	7/8	3/3	4/5
Abdomen	4/12	2/7	2/5
Back	7/14	3/8	4/6
Head & neck	7/8	4/5	3/3
Extremity	1/4	1/3	0/1
Prior medical PN treatments			
Yes/No	12/48	4/25	8/28
Methotrexate/vinblastine	6	3	3
Pirfenidone	3	1	2
Cis retinoic acid	1	-	1
Peginterferon alfa 2b	1	-	1
Thalidomide	1	-	1

Footnotes: [a]There was no significant difference in sex by arm (P= 0.19 by Fisher' exact test). [b]The PN chosen for volumetric MRI analysis to determine time to progression. [c]The PN volume was larger in participants randomized to tipifarnib compared with placebo (P=0.09, exact Wilcoxon rank sum test).
Abbreviations: PN: plexiform neurofibromas.
Source: Widemann et al. 2014[41]

17.7.2 Propensity score analyses supplementary data

Kaplan-Meier curves for the different methods (naïve, weighted, matched 1:1 without replacement, and matched 1:2 with replacement) used in the propensity score analyses described in Section 9.8 are presented in Figure 1 to Figure 4.

Figure 1. Kaplan-Meier data from propensity score analyses (naïve)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/365.25
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including selumetinib.
The values at the base of the figure indicate number of patients at risk. Dots represent censored observations. Patients at risk number represents the sum of stabilised IPTW.
Abbreviations: IPTW: inverse probability of treatment weighting; MEK: mitogen-activated protein kinase; MRI: magnetic resonance imaging; NH: natural history; PFS: progression-free survival.

Figure 2. Kaplan-Meier data from propensity score analyses (weighted)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/365.25
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including selumetinib.
The values at the base of the figure indicate number of patients at risk. Dots represent censored observations. Patients at risk number represents the sum of stabilised IPTW.
Abbreviations: IPTW: inverse probability of treatment weighting; MEK: mitogen-activated protein kinase; MRI: magnetic resonance imaging; NH: natural history; PFS: progression-free survival.

Figure 3. Kaplan-Meier data from propensity score analyses (matched 1:1 without replacement)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/365.25
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including selumetinib.
The values at the base of the figure indicate number of patients at risk. Dots represent censored observations. Patients at risk number represents the sum of stabilised IPTW.
Abbreviations: IPTW: inverse probability of treatment weighting; MEK: mitogen-activated protein kinase; MRI: magnetic resonance imaging; NH: natural history; PFS: progression-free survival.

Figure 4. Kaplan-Meier data from propensity score analyses (matched 1:2 with replacements)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/365.25
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including selumetinib.
The values at the base of the figure indicate number of patients at risk. Dots represent censored observations. Patients at risk number represents the sum of stabilised IPTW.
Abbreviations: IPTW: inverse probability of treatment weighting; MEK: mitogen-activated protein kinase; MRI: magnetic resonance imaging; NH: natural history; PFS: progression-free survival.

17.7.3 Clinical outcome measure assessments

The primary analysis of the clinical outcome measures was based on descriptive statistics and MMRM analyses summarising the changes over time. MMRM analyses were used to allow for correlation between observations within a subject. Supportive analyses using CMTs were conducted to help with interpretation of clinical benefit. Thresholds for meaningful change were estimated using both distribution (one-half standard deviation) and anchor-based (with the GIC as the anchor) approaches. Whenever available, data from published literature were used to define the CMT.[34, 40]

The CMT and statistical methods, as well as the assessments used for the clinical outcome measures are summarised below.[34, 40]

Clinically Meaningful Thresholds

Meaningful change is the ability to measure clinically important change in a clinical state. CMTs were estimated using both distribution- and anchor-based approaches,

supplemented with empirical cumulative distribution function (eCDF) and probability density function (PDF) curves.

For the anchor-based approach, the GIC was used as an anchor, as it asks patients (or legal guardians) to assess changes in pain and other morbidities that can be linked to relevant questions/outcomes from the PROs or functional evaluations at the same follow up evaluations and only after the other measures have been completed. The patient GIC was used for the patient PRO evaluations and the parent proxy GIC was used for the parent-proxy PRO evaluations as they link directly to the patients and parents (or guardian) experience. To support the appropriateness of an anchor, the correlation between the anchor and the PRO or functional evaluation was reported. An anchor was considered adequate if the correlation coefficient was >0.30 (Coon and Cook 2018).

For the distribution-based approach, the half value of the standard deviation of the baseline scores was used.

Whenever available, data from published literature were used to define the CMT.

Statistical methods for PROs

Summary measures of cumulative patient disposition and compliance at each scheduled assessment were derived for all PROs, among those patients who were expected to have PRO assessments. At each post-baseline assessment, the absolute change in scores from baseline was calculated as the post-baseline value minus baseline value for each item, domain and primary PRO as applicable. Not all the PROs have domain categories or the same primary outcome of interest.

For each of the items, the change from baseline values was classified according to the following categories:

- Worsening ≥3 points compared to baseline
- Worsening 2 points compared to baseline
- Worsening 1 point compared to baseline
- Stable
- Improved 1 point compared to baseline
- Improved 2 points compared to baseline
- Improved ≥3 points compared to baseline

A stacked column chart showing the distribution of change in responses at each pre-cycle visit was also provided. The following descriptive analyses were also provided, as applicable:

- Item level

    - Descriptive statistics (counts and percentages) for each response option for each item at each pre-cycle visit; a stacked column chart showing the distribution of responses at each pre-cycle visit was also provided

    - Descriptive statistics (counts and percentages) for each change in response category for each item at each pre-cycle visit; a stacked column chart showing the distribution of change in responses at each pre-cycle visit was also provided

    - Descriptive statistics (N, mean, SD, median, minimum, maximum and percentage missing data) for each item score at each pre-cycle visit

- Domain level or total score

    - A table with descriptive statistics (N, mean, SD, median, minimum, maximum and percentage missing data) for the scores (total score and domain scores if applicable) and a line graph with mean values and corresponding 95% CI for each pre-cycle visit

    - A table with descriptive statistics (N, mean, SD, median, minimum, maximum and percentage missing data) for the change from baseline in scores (total score and domain scores if applicable) and a line graph with mean change from baseline values and corresponding 95% CI for each pre-cycle visit

    - Descriptive statistics (counts and percentages) for patients with improvement/no change/deterioration (as defined by the various CMTs) at each pre-cycle visit. The 95% confidence interval for a single binomial proportion are also provided

Change from baseline in the primary outcome scores were also analysed using a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) analysis. The primary objective of this analysis was to examine the change from baseline at pre-Cycle 13. The response variable was the change from baseline to each pre-cycle C, with C=3, 5, 9, 13 and 25. The model included terms for pre-cycle visit, baseline score, age, the number of morbidities at baseline and baseline Visit X pre-cycle interaction. The model will present least squares (LS) mean estimates, standard errors, 95% CIs and p-values for mean changes from baseline to each pre-cycle visit.

Statistical methods for functional evaluations

The following descriptive analyses were also provided, as applicable:

- A table with descriptive statistics for the observed values and the change from baseline in functional outcome as applicable; a line graph with mean of change from baseline values and corresponding 95% CI for each pre-cycle visit

- Descriptive statistics (counts and percentages) for patients with improvement / no change / deterioration at each pre-cycle visit. The 95% confidence interval for a single binomial proportion are also provided

- Change from baseline in the primary outcomes were further analysed using a MMRM

Table 76. Summary of assessed clinical outcomes, instruments and CMT approaches[34]

Outcome	Instrument	Type of evaluation	CMT approach
HRQoL	PedsQL	PRO	Anchor Distribution-based Literature (Varni et al. 2003)
Pain	NRS-11	PRO	Anchor Distribution-based Literature (Farrar et al 2000, Kendrick and Strout 2005, Salaffi et al 2004, Voepel-Lewis et al 2011)
	PII	PRO	Anchor Distribution-based
Motor function	Strength Range of motion	Functional	Anchor Distribution-based
	PROMIS	PRO	Anchor Distribution-based Literature (Thissen et al 2016)
	Grooved pegboard	Functional	Anchor Distribution-based
	Leg length evaluation	Functional	Anchor Distribution-based
Airway function	Sleep study PFT	Functional	REiNS literature (Plotkin et al 2016)
Bowel/bladder function	DVQ	PRO	Anchor Distribution-based
Visual function	Acuity testing Exophthalmometry	Functional	REiNS literature (Fisher et al 2013)
Disfigurement	Photography	NA	NA
Physical function	6MWT	Functional	Literature (Harmatz et al 2018)

Abbreviations: 6MWT: 6-minute walk test; DVQ: Dysfunctional Voiding Questionnaire; NRS-11: Numerical Rating Scale 11; PFT: pulmonary function test; PII: Pain Interference Index; PRO: patient-reported outcome; PROMIS: Patient-reported Outcome Measurement Information System.

HRQoL (PedsQL)

General HRQoL was measured using the generic PedsQL™ 4.0 Generic Core Scales. The generic PedsQL assesses function in 4 domains: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items) and 4) School Functioning (5 items). Each item is scored on a 5-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). For patient-reported and parent/guardian-reported measures, which will be analysed separately, items are reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQoL. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale were missing, the scale score was not computed.[140] A Total Scale Score was also

derived as the sum of all the items divided by the number of items answered on all the scales. In addition, scale scores were calculated using the raw item scores (without the linear transformation but still reversed).

The primary outcomes for HRQoL were the Total Scale Score of the patient-reported PedsQL for children >8 years of age and the Total Scale Score of the parent/guardian-reported PedsQL administered to parents/guardians of children ≥2 years of age. Secondary outcomes for HRQoL were the mean scores of the 4 domains (physical, emotional, social and school) of the patient-reported scale completed by children >8 years of age and the 4 domain mean scores from the parent/guardian-reported PedsQL administered to parents/guardians of children ≥2 years of age.

In addition, patients were classified with impaired global HRQoL (Yes/No) at each pre-cycle visit, using the linearly transformed scores. Patients were classified with impaired global HRQoL if their total or domain scores fell 1 standard deviation below the population sample mean as reported by Varni et al. 2003.[140]

PedsQL was evaluated based on descriptive statistics and MMRM model as described above.

Pain (NRS-11, PII, pain medication survey)

Pain intensity was measured by the NRS-11, consisting of four questions scored on a scale 0=no pain to 10=worst pain you can imagine. The primary outcome for the self-report NRS-11 was the rating of 1 specific PN pain (e.g. the “target tumour”) by children ≥8 years of age. This pain rating was for the physician-selected target PN for the patients who were administered this item. Patients who had their baseline evaluation using the earlier version of the NRS-11 (Version 1), which did not specifically indicate the physician-selected target PN, were included in the primary outcome analysis if the self-selected PN and physician-selected PN matched. The revised version (Version 2) was used for all patients enrolled from November 2015. The same PN pain was rated across all study pre-cycles.

Pain intensity was evaluated based on descriptive statistics and MMRM model as described above. Further to these, pain palliation was also defined for the primary outcome and was based on 2 related components: 1) reduction in pain intensity and 2) stability or reduction in analgesic use. Two definitions for the pain palliations were considered. The first definition included only symptomatic patients (i.e. with a pain score ≥X points at baseline where X corresponded to the value of 2, 1 or the CMT derived from the study). The second definition of pain palliation was considered to include the asymptomatic patients. Both definitions also considered the stability or reduction in analgesic use. Information on all analgesics used by patients in pain control was collected on the pain medication survey as well as on the concomitant medication form.

Time to pain palliation was defined as the time from the first dose of study drug until the date of the first observed pain palliation.

Pain interference was measured by the PII. The PII is a 6-item scale that assesses the extent to which pain has interfered with an individual’s daily activities in the past seven

days. Items are rated on a 7-point Likert scale (0=not at all to 6=completely), and the total score is the mean of the completed items. The total score was computed if at least 50% of items were answered (e.g. 4 out of 6). Higher scores indicated more interference with daily activities. Pain interference was evaluated based on descriptive statistics and MMRM model as described above.

Motor function (PROMIS, strength, range of motion, grooved pegboard test, grip strength and key pinch, leg length evaluation)

Analysis of motor function included only those patients with a motor morbidity at enrolment, with the exception of leg length discrepancy analysis and grooved pegboard analysis that included only those patients with lumbarsacral plexus/lower limb PN or aged ≥5 years at enrolment with cervical/upper thoracic/upper limb, respectively.

The motor function in all motor morbidity patients were assessed using the PROMIS Pediatric Short Form v1.0 – Mobility 8a and PROMIS Pediatric Short Form v1.0 – Upper Extremity 8a. These forms assessed level of motor function over the past 7 days. PROMIS Physical Functioning Scales assessed the domains of Mobility and Upper Extremity Function and included mobility items such as 'I could walk upstairs without holding on to anything' and upper extremity items such as 'I could button my shirt or pants'. Parent proxy items are parallel to child items. The short forms consisted of 8 items using a 5-point Likert scale format (i.e. 0=unable to do, 4=can do without any difficulty). Raw scores were converted to T–scores, which are based on reference data from the US general population, where mean=50, SD=10. Both raw and T-scores were analysed separately. Higher scores indicated better physical functioning. Change from baseline in the mobility and upper extremity scores were further analysed using a MMRM in a similar way as described above.

All patients with PN that caused motor dysfunction, weakness or cord compression underwent evaluation of strength of all muscle groups and evaluation of range of motion (ROM) of all joints at baseline. Patients with PN located in the lumbosacral plexus or below (i.e. lower limb) underwent leg length measurements, to evaluate for discrepancy. Patients aged ≥5 years at enrolment with PN located in the upper extremities or patients with known cervical or upper thoracic cord compression underwent Grooved Pegboard Testing.

The primary outcomes for assessing motor function were strength for each muscle group (scale of 0 to 5 using the Medical Research Council scale) and ROM for each joint (measured in degrees). The following test results were secondary outcomes:

- Grip and Key pinch (kg)
- Leg length discrepancy (cm) in patients with lumbarsacral plexus/lower limb PN
- Grooved Pegboard in patients aged ≥5 years at enrolment with cervical/upper thoracic/upper limb (time to complete in seconds, z-score, number of pegs dropped, for dominant and non-dominant hand).

Each joint (ROM) and muscle group (strength) was allocated, based on anatomical location of the PN, to a location quadrant:

- Upper or Lower
- Right or Left or Bilateral

A strength score was derived as the average strength of all muscles in the same body quadrant as the target PN. Similarly, the ROM score was calculated as the sum of all the degrees of movement for each of the joints in the same quadrant as the target PN; higher ROM scores indicate more degrees of movement.

Motor function was evaluated based on descriptive statistics and an MMRM model, as described above. For ROM, pre-cycle assessments where a patient had the same number of joints as at baseline were included in the analysis.

Airway function (AHI sleep study, PFT)

Analysis of airway function includes only those patients with an airway morbidity at enrolment. All patients with airway PN (upper airway / extrathoracic and lower airway / intrathoracic) underwent functional evaluations, including sleep studies, evaluation of endurance using the 6MWT and PFTs. Patients who had a tracheostomy, which bypassed the airway obstruction caused by the PN, did not require a sleep study and did not perform PFTs.

While each of these tests generated multiple measurements of airway function, the primary outcome for this analysis was the AHI (events per hour), FEV1 (litres) and R20 (resistance). For pre-school children, FEV0.75 was used in place of FEV1.

At each post-baseline assessment, the absolute change from baseline was calculated for AHI, in FEV1 (litres) or FEV0.75 (for pre-school children) and R20 (resistance). In addition the percentage change from baseline was calculated for FEV1 (litres) or FEV0.75 (for pre-school children) and R20 (resistance).

A percentages change of ≥12% in FEV1 (litres) or FEV0.75 (for pre-school children) were classified as improvements, as recommended by the REiNS functional group (Plotkin et al 2016). Functional improvement was defined as ≥20% decrease in R20; the REiNS functional group recommended this threshold for R10, but R20 was used in this study.

Patients were further classified as having sleep disturbance ('Yes/No') at each pre-cycle visit if the AHI was >1. In addition, for patients with an AHI >5 at baseline, improvement / no change / deterioration at each pre-cycle visit was derived using the thresholds reported by Plotkin et al.[87]

Airway function was evaluated based on descriptive statistics and an MMRM model, as described above.

Bowel/bladder function (DVQ)

Bowel and bladder functionality was measured with the DVQ (Afshar et al. 2009). The DVQ was only completed by patients (aged ≥8 years) or by the parent/guardian of a patient with bowel and/or bladder morbidity; therefore, the analysis only included patients with bowel and/or bladder morbidity at enrolment.

This questionnaire contains 14 items; the last question (item 14) requested feedback on the ease of completing the questionnaire and was not included in the total score. Scores of ≥11 (out of 52) were demonstrated as the threshold for bowel and bladder dysfunction in the initial validation study performed on this questionnaire (Afshar et al 2009). The absolute change in DVQ score from baseline was calculated as each post-baseline value minus baseline value.

Bowel/Bladder function was evaluated based on descriptive statistics and an MMRM model as described above.

Visual function (visual acuity, exophthalmometry)

Analysis of vision function includes only those patients with a vision morbidity at enrolment. The analysis outcomes for patients with vision morbidity were visual acuity and the extent of exophthalmos.

Visual acuity was measured using HOTV or, if the patient was too young to reliably perform HOTV testing, Teller Acuity Cards. HOTV was reported in logMAR and Teller Acuity was recorded in cycles/cm, which was converted to logMAR by the study team. Exophthalmos was measured using exophthalmometry (in mm).

The post-baseline changes in exophthalmometry and change using the logarithm of the minimum angle of resolution (logMAR) were classified as improvement / no change / deterioration according to baseline score at each pre-cycle visit. A decrease in logMAR of more than 0.2 and a decrease in exophthalmos of more than 2 mm were considered clinically meaningful improvements, as recommended by the REiNS functional group.[177]

Visual function was evaluated based on descriptive statistics and an MMRM model as described above.

Disfigurement (photography)

Disfigurement was measured by standardised photography (videography could also have been used to assess for disfigurement and function/movement in some patients). Photographs and videography had to undergo anonymisation to respect patient privacy and abide by legal requirements. Standardised photography was performed on all patients who had disfigurement assigned as a PN-related morbidity at baseline and at all re-staging visits.

There was no formally planned method of assessing changes in disfigurement.

Physical function (6MWT)

All patients ≥5 years of age at enrolment, with lower extremity PN, cord compression or airway PN (including patients with tracheostomy, providing they can walk independently), underwent endurance testing using the 6MWT.

The absolute change from baseline was calculated as each post-baseline value minus baseline value. A threshold for clinically meaningful improvement was defined for the 6MWT distance using literature-recommended values (Harmatz et al 2018); this was used to classify the post-baseline changes as improvement (absolute change ≥30 metres) / deterioration (absolute change ≥-30 metres) / no change (otherwise) according to baseline score at each pre-cycle visit.

The 6MWT was evaluated based on descriptive statistics and MMRM model as described above.

17.7.4 TTO study details

Health state vignettes

The number of health states was limited to nine to ensure that the TTO interview length was acceptable. An overview of the health states is summarised in Table 77.

Table 77. Overview of health states

Health states	Patient profiles		
	Treatment status	Age	PN location
S1	Untreated (off-selumetinib))	Child	Unspecified (generic)
S2	Untreated (off-selumetinib)	Child	Face
S3	Untreated (off-selumetinib)	Child	Trunk
S4	Untreated (off-selumetinib))	Child	Leg
S5	Untreated (off-selumetinib)	Adult	Unspecified (generic)
S6	Treated (on-selumetinib)	Child	Unspecified (generic)
S7	Treated (on-selumetinib)	Child	Face
S8	Treated (on-selumetinib)	Child	Trunk
S9	Treated (on-selumetinib)	Child	Leg

Abbreviations: PN: plexiform neurofibroma; S1–9; states 1–9.

Vignette development interview guide

Introduction

Good (morning/afternoon/evening), my name is [insert name] and I am a researcher at Acaster Lloyd Consultancy Ltd. Thank you for taking the time to participate in this interview. The purpose of this conversation is to understand the impact that neurofibromatosis type 1 (NF1) with plexiform neurofibroma (PN) has on individuals with this condition.

More specifically, we are looking to develop descriptions of people with NF1-PN for the general public. These descriptions should describe what might be typical and will vary by PN location and disease progression.

The purpose of today's interview is to help us develop these descriptions. The severity of each description is supposed to be fair, typical and representative.

he results will be anonymous; your identity will not be disclosed and all information you provide will remain confidential. Your participation is voluntary, so you can stop participating at any time without giving us a reason.

We will be recording this interview, so we don't miss any of your comments. Can I check that this is okay with you? [If yes] Okay, thank you. I'll start recording now.

Background questions

First a few background questions about your professional experience with NF1-PN.

- Please tell us a bit about your role
- How long have you been working with patients with NF1-PN?
- How many patients with NF1-PN do you have under your care?
- How often do you typically see a patient with NF1-PN?

General feedback on the vignettes

We will discuss descriptions of NF1-PN patients with you, although we do not mention the condition in the text for methodological reasons.

I am now going to move on to the next part of the interview, where I would like to find out your views about draft descriptions of someone with NF1-PN. I am interested in hearing your feedback on the accuracy of the description that we have sent to you in an email.

- Do you have this description in front of you?

MODERATOR NOTE: GO OVER HEALTH STATES LINE BY LINE. PROBE FOR THINK-ALOUD FEEDBACK.

- What are your overall impressions of the descriptions of someone with NF1-PN?
- How do these descriptions of someone with NF1-PN fit with your experience?
- Are the descriptions too severe or extreme? Alternatively, does it understate what people with NF1-PN experience?

- In our description of the impact of NF1-PN we have a number of bullet points. Could we review each bullet in turn? Too severe/extreme or understated? Fair representation overall? Appropriate? What is missing?

- We also describe the psychological and social impact on people with NF1-PN. Do you think this is a fair description from your experience?

- Comparing the health state descriptions, do you think the differences in the descriptions accurately reflect the differences you would expect between patients with these characteristics?

- Are there any other impacts that we have missed?

- Is there anything else that seems incorrect?

Specific feedback on the vignettes

MODERATOR NOTE: ONLY INCLUDE THESE QUESTIONS IF THEY ARE NOT COVERED SPONTANEOUSLY IN THE GENERAL FEEDBACK ON VIGNETTES.

Visual impairment (vignettes 2 and 6; facial PN)

- Can you describe how visual impairment typically manifests in patients with PN?

- How common is visual impairment in patients with facial PN?

- Do patients typically experience total vision loss or partial visual impairment? In one eye or both?

- Do you believe visual impairment associated with facial PN is something that can improve with treatment?

Movement restriction in patients with facial PN (vignettes 2 and 6)

- To what extent do patients with facial PN experience restrictions in their movement?

- If patients with facial PN experience restricted movement, is this typically only in their face or can other areas of movement be affected? If so, which areas typically are restricted?

Bowel and bladder incontinence (vignettes 3 and 7)

- How sever is bowel or bladder incontinence typically in people with NF1-PN?

- How common is incontinence for people who have PN located within their trunk? Which is most common – bowel or bladder incontinence?

Daily activities (all vignettes)

- All of the descriptions describe patients sometimes needing help looking after themself (e.g., getting dressed). Do you believe this reflects typical patients with NF1-PN?

- What other, if any, daily activities can people with NF1-PN have difficulty with?

- Do the types of activity that people with NF1-PN have difficulty with vary by PN location? If so, how (general patients, face, trunk, extremity).

Cognitive function (all vignettes)

- All of the descriptions describe patients experiencing some problems with memory and attention and requiring some support with daily activities, such as work/education and maintaining social relationships. Do you believe this reflects typical patients with NF1-PN?

- How common are cognitive difficulties in patients with NF1-PN?

- Can you describe some of the cognitive difficulties that are experienced by patients with NF1-PN?

Independence (vignette 9)

- The untreated adult vignette describes patients becoming more independent, managing their daily activities and care. To what extent do adults with NF1-PN have difficulties reaching independence?

- What kind of activities might adults with NF1-PN need support with?

Close of interview

We have now come to the end of the interview.

Before I stop the recorder, do you have any further comments about the description or your experience of having NF1-PN?

Okay, great. Thank you very much for your participation.

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under [redacted] and information submitted under [redacted].

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies (HST)

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Clarification questions

September 2021

File name	Version	Contains confidential information	Date
ID1590_Selumetinib_ERG Clarification Questions_ Responses_[ACIC]	1.0	Yes	24th September 2021

Section A: Clarification on effectiveness data

Literature searches

A1. Priority question. The Evidence Review Group (ERG) noted an error in the line combinations in the Embase search (Table 3, Appendix 1): Line #52 ("conference abstract" or "conference review").pt. was limited in #53 to papers published between 1974-2018 (limit 52 to yr="1974-2018"). However, when the facet for excluded terms was combined in line #57, line #52 has been included in error, instead of just #53, this means that all conference proceedings will have been excluded and not just those published before 2018.

Please rerun this aspect of the search and ensure that no relevant papers have been missed.

AstraZeneca acknowledges this search term error and provide the updated search below and confirm that no relevant papers have been missed.

The search strategy included in the HST submission document contained this error due to inclusion of an erroneous table whilst writing the submission. However the search terms used to query Embase were correct and did not exclude conference proceedings. The below table is the accurate Embase search strategy, conducted on 26th January 2021. This strategy included all conference abstracts published from 1st January 2017 onwards.

Table 1. Search terms used in Embase (Searched via Ovid SP on 26th January 2021)

	#	Searches	Results
Disease area: NF1 PN	1	exp neurofibromatosis type 1/	3,605
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kw.	10,295
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kw.	12,188
	4	or/1-3	17,002
	5	neurofibroma/	6,342
	6	(plexiform neurofibroma$ or plexiform neuroma$).ti,ab,kw.	1,605
	7	or/5-6	7,001
	8	4 and 7	2,333
Study design: RCTs	9	"randomized controlled trial (topic)"/	194,891

	10	randomized controlled trial/	641,842
	11	clinical trial/	998,361
	12	exp "clinical trial (topic)"/	344,523
	13	controlled clinical trial/	466,048
	14	multicenter study/	276,039
	15	randomization/	89,812
	16	single blind procedure/	41,600
	17	double blind procedure/	180,633
	18	crossover procedure/	65,906
	19	placebo/	361,846
	20	phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	170,780
	21	(clinical adj trial$).ti,ab,kw.	574,705
	22	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kw.	247,642
	23	placebo$.ti,ab,kw.	321,323
	24	(allocat$ adj2 random$).ti,ab,kw.	45,713
	25	(Randomi?ed adj2 trial$).ti,ab,kw.	463,855
	26	rct.ti,ab,kw.	42,617
	27	or/9-26	2,484,002
Study design: Non-RCTs/observational studies	28	exp epidemiology/	3,604,639
	29	exp case control study/	185,272
	30	exp cohort analysis/	662,004
	31	Case control.ti,ab,kw.	173,389
	32	(cohort adj (study or studies)).ti,ab,kw.	334,387
	33	cohort analy$.ti,ab,kw.	14,180
	34	(Follow up adj (study or studies)).ti,ab,kw.	68,688
	35	(observational adj (study or studies)).ti,ab,kw.	183,647
	36	Longitudinal$.ti,ab,kw.	379,488
	37	retrospective$.ti,ab,kw.	1,318,938
	38	Cross sectional.ti,ab,kw.	502,416
	39	Cross-sectional study/	390,149
	40	exp Longitudinal study/	150,464
	41	exp follow up/	1,637,236
	42	exp retrospective study/	1,021,601
	43	exp observational study/	220,005
	44	(Prospective adj (study or studies)).ti,ab,kw.	274,022

	45	(evaluation adj (study or studies)).ti,ab,kw.	8,667
	46	(epidemiologic adj (study or studies)).ti,ab,kw.	34,755
	47	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kw.	12,631
	48	(Open-label adj (trial$ or stud$)).ti,ab,kw.	20,398
	49	Non-blinded stud$.ti,ab,kw.	193
	50	(chart adj3 review).ti,ab,kw.	87,083
	51	or/28-50	6,646,318
Exclusion terms	52	("conference abstract" or "conference review").pt.	4,005,664
	53	limit 52 to yr="1974-2017"	3,038,161
	54	exp animals/ not exp humans/	4,750,859
	55	(comment or editorial).pt.	682,497
	56	historical article/	1
	57	or/53-56	8,180,843
Combined	58	8 and (27 or 51)	772
	59	58 not 57	**660**

A2. Priority question. The ERG noted a potential error in the Database of Abstracts of Reviews of Effects (DARE) search (Table 5, Appendix 1). Line #4 MeSH DESCRIPTOR Neurofibroma, appears to have been combined in error in line #7 with terms for neurofibromatosis type 1 (NF1), rather than in line #8 with terms for plexiform neurofibroma (PN) as had been done in the previous Medline, Embase and Cochrane searches.

Please rerun and check that no additional relevant studies have been missed.

AZ acknowledges this search error and provide updated search below and confirm that no additional relevant studies have been missed.

Table 2. Search terms for DARE (searched via the University of York CRD platform on 6th September 2021)

#	Searches	Results
1	MeSH DESCRIPTOR Neurofibromatosis 1 EXPLODE ALL TREES	2
2	((neurofibroma* adj1 ("1" or i or peripheral or von Recklinghausen)))	6
3	((NF1 or NFI or NF-1 or NF-I))	5
4	(#1 OR #2 OR #3)	6

5	MeSH DESCRIPTOR Neurofibroma	3
6	MeSH DESCRIPTOR Neurofibroma, Plexiform	0
7	((plexiform neurofibroma* or plexiform neuroma*))	1
8	(#5 OR #6 OR #7)	3
9	(#4 and #8)	2
10	(#9) IN DARE	**0**

Database: DARE, the most recent issue searched was Issue 2 of 4, April 2015

A3. Please justify the use of highly specific search strategies which focus on only patients with inoperable PN associated with NF1 for the disease facet. Whilst this correctly reflects the scope, given the low number of hits retrieved the combination of terms for NF1 and PN and study design filters may have been overly restrictive.

The clinical SLR search strategy was not limited by terms for 'inoperable', ensuring that the strategy would not be too restrictive. The strategy combined broad term groups for NF1, PN, and published study filters to ensure the search was suitably specific given the focus of the scope on NF1 patients with PN.

A4. There appears to be a disparity between the number of conference results reported in the PRISMA diagram (Figure C1; n=1,083) and in the searches reported in Appendix 1, Table 6 (n=1104).

Please confirm the correct number of conference results.

The PRISMA diagram was accurate, but the number of conference results reported in Appendix 1, Table 6 was incorrect. A corrected version of Table 6 is presented below.

Table 3. Search strategies for congress searching (performed between 21st January 2021 and 5th February 2021)

Conference	Link	Search Strategy	Number screened; included
ASCO Annual Meeting: 2018	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: **Meeting:** ASCO Annual Meeting **Date:** 2018 The following string was then searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR	40 screened; 0 included

		Keywords:"plexiform" OR Keywords:"von Recklinghausen")	
ASCO Annual Meeting: 2019	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: **Meeting:** ASCO Annual Meeting **Date:** 2019 The following string was then searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:"von Recklinghausen")	57 screened; 0 included
ASCO Annual Meeting: 2020	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: **Meeting:** ASCO Virtual Scientific Program **Date:** 2020 The following string was then searched for using the Advanced Search function: (Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:"von Recklinghausen")	47 screened; 0 included
ASPHO 2018	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM18&ssoOverride=OFF&USERPID=PUBLIC	The 2018 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	2 screened; 0 included
ASPHO 2019	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM19	The 2019 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1"	3 screened; 0 included

	&ssoOverride=OFF&USERPID=PUBLIC	• NF1 • Plexiform • Von Recklinghausen's	
ASPHO 2020	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM20&ssoOverride=OFF&USERPID=PUBLIC	The 2020 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	4 screened; 1 included
Children's Tumor Foundation NF Conference: 2019[a]	https://www.ctf.org/get-involved/nf-conference	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	145 screened; 3 included
Children's Tumor Foundation NF Conference: 2020[a]	https://www.ctf.org/get-involved/nf-conference	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	59 screened; 3 included
ESMO Congress 2018	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress	The 2018 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	6 screened; 0 included
ESMO Congress 2019	https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress	The 2019 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	14 screened; 0 included

ESMO Congress 2020	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020	The 2020 conference website was searched in turn for the following terms: • Neurofibrom* • "NF-1" • NF1 • Plexiform • Von Recklinghausen's	5 screened; 0 included
ISPNO: 2018[b]	http://ispno2018.com/	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	356 screened; 0 included
ISPNO: 2020[b]	http://ispno2020.umin.jp/	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	49 screened; 0 included
ISPOR Annual European Meeting 2018	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2018-11, ISPOR Europe 2018, Barcelona, Spain" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual European Meeting 2019	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field, selecting "2019-11, ISPOR Europe 2019, Copenhagen, Denmark" under the dropdown 'Conference' menu: • Plexiform neu* • NF-1 • NF1	0 screened; 0 included

		• Neurofibrom* • Von Recklinghausen's	
ISPOR Annual European Meeting 2020	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the “Keyword” field, selecting “2020-11, ISPOR Europe 2020, Milan, Italy” under the dropdown ‘Conference’ menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual International Meeting 2018	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the “Keyword” field, selecting “2018-05, ISPOR 2018, Baltimore, MD, USA” under the dropdown ‘Conference’ menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual International Meeting 2019	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the “Keyword” field, selecting “2019-05, ISPOR 2019, New Orleans, LA, USA” under the dropdown ‘Conference’ menu: • Plexiform neu* • NF-1 • NF1 • Neurofibrom* • Von Recklinghausen's	0 screened; 0 included
ISPOR Annual International Meeting 2020	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the “Keyword” field, selecting “2020-05, ISPOR 2020, Orlando, FL, USA” under the dropdown ‘Conference’ menu: • Plexiform neu* • NF-1 • NF1	5 screened; 0 included

		• Neurofibrom* • Von Recklinghausen's	
JGNC 2018[a]	http://www.nf-paris2018.com/EventPortal/Information/NF2018/WELCOME.aspx	The abstract book in PDF format was searched using the 'Ctrl + F' function, to search the following terms one by one: • Type 1 • NF-1 • NF1 • Von Recklinghausen's	291 screened; 5 included

Footnotes: [a]In 2018, the Children's Tumor Foundation NF Conference was combined with the European Neurofibromatosis Meeting and ran as JGNC 2018; [b]biennial conference
Abbreviations: ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; ESMO: European Society for Medical Oncology; FL: Florida; ISPNO: International Symposium on Pediatric Neuro-Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; JGNC: Joint Global Neurofibromatosis Conference; LA: Louisiana; MD: Maryland; NF1: type 1 neurofibromatosis; USA: United States of America.

Patient pathway

A5. The National Institute for Health and Care Excellence (NICE) scope specified that the treatment will be used for patients who have symptomatic and inoperable PN.

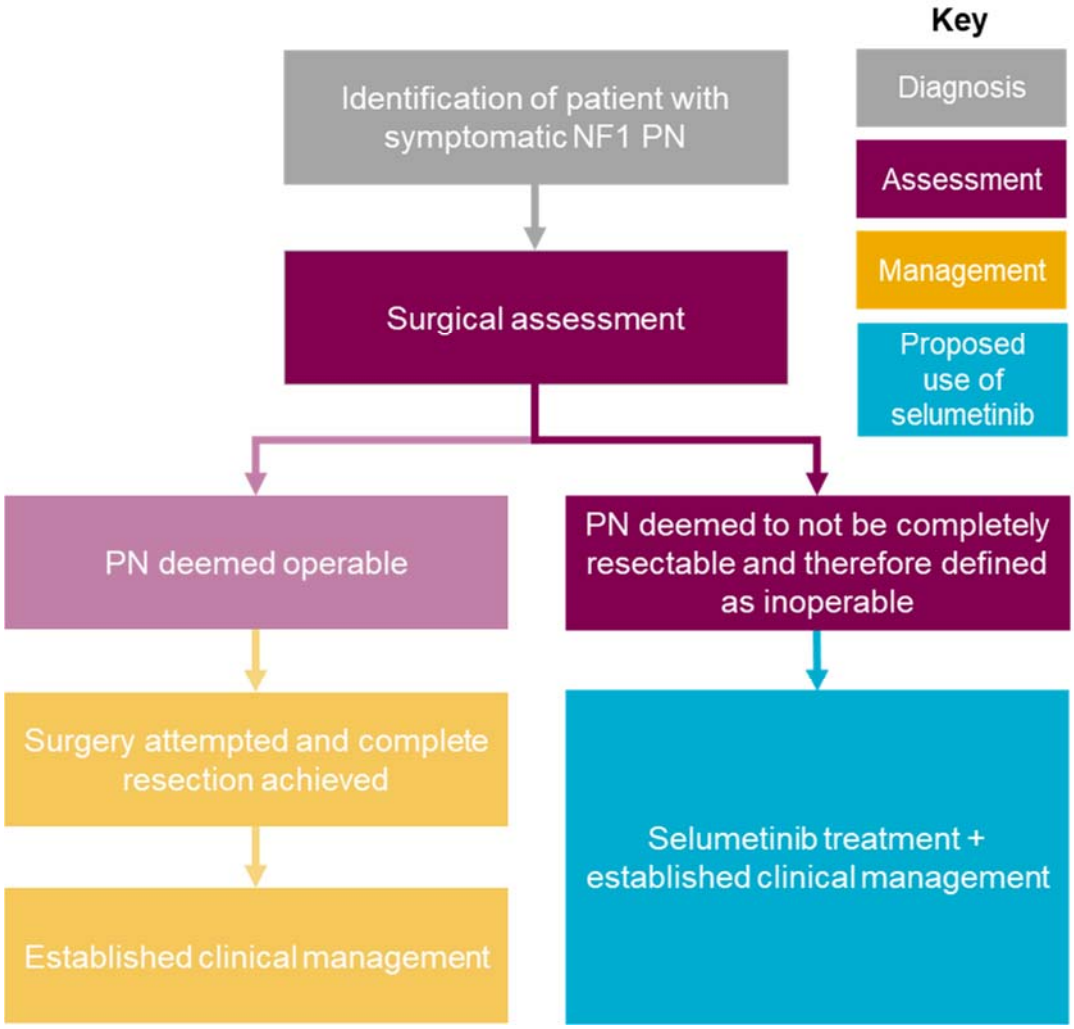
Please clarify why, according to Figure B7, the treatment is proposed to be used for patients with symptomatic PN expected to be partially resected.

Surgery is only considered for NF1 patients in the UK where complete resection is achievable and there is positive risk/benefit balance, otherwise they are considered inoperable.

In UK clinical practice, surgery is not typically considered for NF1 unless a PN causes functional or cosmetic issues, due to the associated risks of surgery proximal to key nerves and blood vessels.[1]

This is also reflected in the SPRINT Phase II Stratum I, an inoperable plexiform neurofibroma (PN) was defined as one which 'could not be completely resected without risk of substantial morbidity due to encasement of or close proximity to vital structures, invasiveness or high vascularity'.[2] Under this definition, PN for which only partial resection can be achieved are considered 'inoperable'. Therefore, patients with symptomatic PN which are expected to be partially resected would be classified as inoperable and would be eligible for selumetinib treatment. Figure B7 has been updated below to further clarify this (Figure 1; please see 'PN deemed to be inoperable').

Figure 1. Pathway for the treatment of NF1-related PN with selumetinib



Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibromas.
Source: AstraZeneca Data on File (SPRINT protocol);[2] Ferner et al. 2007.[3]

Systematic literature review (SLR)

A6. The process of critical appraisal of the studies is not reported in the company submission (CS).

Please provide the details of the process, including the tool used, the number of reviewers, and how disagreement was resolved.

The critical appraisal tool used was taken from the NICE HST submission template and assigned based on study design. All studies captured in the SLR were non-randomised studies, and were therefore appraised via the NICE adapted version of the Critical Appraisal Skills Programme (CASP) tool.[4]

Quality assessments were conducted by one independent reviewer and verified by a second independent reviewer. Any discrepancies identified by the second reviewer

was discussed by both individuals and if necessary, a third independent reviewer was enlisted to arbitrate the final decision.

A7. Table C1 of the CS reported the selection criteria for published studies.

a) Please specify if patients with PN that can be partially resected were included or excluded from SLR. Please justify the approach.

b) Please provide more information if (1) disfigurement, (2) visual and (3) airway functioning, (4) bowel and bladder continence were included or excluded as outcomes for the SLR. Please justify why considering that the outcomes were listed in the NICE scope.

c) Please justify why congress abstracts published before 1st January 2018 were excluded from the SLR.

d) Language restrictions include *"publications with at least an abstract in the English language"*. Please clarify what happened with the studies with an English language abstract which were considered to be eligible. Please provide information on how many studies were found.

a) Approach for patients with partially resectable PN

Patients with PN that could be partially resected were considered as relevant and included in the SLR, in line with the definition and rationale provided in the response to question A5.

b) Disfigurement, visual functioning, airway functioning and bowl and bladder continence outcomes

The list of clinical outcomes presented in the eligibility criteria is not exhaustive; all clinical outcomes were considered as relevant and included in the SLR. Disfigurement, visual and airway functioning, and bowel and bladder continence were therefore considered relevant outcomes in this SLR and were extracted where reported.

c) Congress abstract inclusion cut-off date

Conference abstracts published before 1st January 2017 were excluded from the SLR (note the corrected Embase search strategy available in Table 1). These were excluded from the SLR on the basis that any high-quality research presented at a conference prior to this date would subsequently have been published in a journal article, and therefore captured in the SLR database searches.

d) Approach for publications with an English language abstract

Any studies with only the abstract in the English language would have been appraised against the eligibility criteria based on the information available in the abstract alone, and if the record was considered relevant for inclusion, the data available in the English abstract would have been extracted. The SLR did not identify any relevant studies with only the abstract in the English language.

A8. According to section 9.4.1, SPRINT Phase II Stratum I was considered of greatest relevance to the decision problem. However, Table C3 lists further relevant studies.

Please elaborate why other studies listed in Table C3, e.g. Baldo 2020 and Epirito-Santo 2020, were not considered to be relevant for inclusion.

All studies listed in Table C3 were considered relevant for inclusion. Full extractions of these studies were reported in Appendix 2 of the submission.

Trials and data analysis

A9. Priority question. The latest data are available from the data cut-off of 29th March 2019, however, section 9.4.2 the CS states that the most recent data cut-off was 27th February 2021.

a) **Please provide more information when the data from the latest timepoint will be available for to present and analyse.**

b) **According to section 9.8.1, describing propensity score analyses, analyses *"were based on the PFS* [progression-free survival] *data reported in the SPRINT CSR* [clinical study report] *(DCO* [data cut-off] *29th June 2018)"*. Please elaborate why this data point was used for the analyses and provide results for the latest available data cut.**

c) **Please provide further details on adverse events (AEs), e.g. provide common AEs >5% and >10%, similar to what is provided in Table C24 of the CS.**

a) Availability of data from the latest timepoint

SPRINT Phase II Stratum I is an ongoing study, being conducted by the National Cancer Institute (NCI) Paediatric Oncology Branch (POB). The NCI therefore provides trial data to AstraZeneca for analysis, following data cuts.

Correspondingly, AstraZeneca have conducted statistical analyses of data from the 29th June 2018 DCO, which are presented within the SPRINT Phase II Stratum I clinical study report (CSR).

In addition, NCI has previously published data from the 29th March 2019 DCO (Gross et al. 2020)[5] and presented data from the 27th February 2021 DCO at the Children's Tumor Foundation 2021 Virtual NF Conference.[6] This final data cut has not been made available to AstraZeneca for use in regulatory or reimbursement interactions; however, the results presented are consistent with previous DCOs, as well as the data used in the cost-effectiveness analysis. For example median time to best response was reported to be 16 cycles and responses were durable in 28 patients; for patients with progressive disease, median time to progression was 36 cycles (range, 16–48 cycles) and the median PFS for the entire cohort had not yet been reached.[6] The results reported for the 29th March 2019 DCO were highly comparable. The median time to best response reported was also 16 cycles (range, 4–36 cycles) and of the 35 patients who had confirmed partial response to selumetinib, 28 (80%) had a durable response; median PFS had not been reached, with a probability of being progression-free of 84%.[5]

Following the very recent receipt of data from the 31st March 2021 DCO rather than the 27th February 2021 DCO from the NCI, AstraZeneca have just begun the process of performing the required biostatistical analyses in order to produce an updated CSR. It is anticipated that the updated CSR will be available by the Q2 2022.

b) Data cut used in propensity score analyses

Data from DCO 29th June 2018 were used for the propensity score analyses. Data from the Gross et al. 2020 publication (DCO 29th March 2019) could not be used for the propensity score analyses, as the validated efficacy dataset, including the individual patient data required for the analyses, is not available to AstraZeneca.

As previously mentioned, data from the 31st March 2021 DCO are in the process of being analysed by AstraZeneca, with the CSR anticipated to be available by Q2 2022. Even if we update the propensity score analysis, the results of an updated analysis would not be anticipated to significantly differ from the analysis conducted with DCO 29th June 2018 data as the majority of SPRINT Phase II Stratum I patients remain progression free, while a majority of Natural History study patients have progressed:

- [redacted]% of patients remained progression free at DCO 29th June 2018[7]
- 84% of patients remained progression free at DCO 29th March 2019 (3 years)[5]
- Median PFS had still not been reached by DCO 27th February 2021 (11/50 patients had progressed at this DCO)[8]

c) Further details of AEs from the 90-Day Safety Update (90DSU)

Full details of adverse events of any grade experienced by >10% of patients are included in Table 4 (90-day safety update; 29th March 2019 DCO). Details of adverse events of any grade experienced by >5% of patients are not available, however, full details of all AEs are provided in the individual patient reports.[9] At DCO 27th February 2021, the most common AEs continued to include gastrointestinal symptoms, asymptomatic creatine phosphokinase increase, paronychia and acneiform rash.[6]

The majority of PN are symptomatic, and are associated with a wide range of morbidities affecting multiple organ systems.[10-13] Selumetinib demonstrates an acceptable safety profile in light of the severity of the disease. While a wide range of AEs were experienced by >10% of patients, the majority of the AEs observed in were mild or moderate in severity and not all may have been treatment related.[7] AEs could generally be managed using dose interruptions, symptomatic or supportive care, rather than through treatment discontinuation, and subsequently resolved. SAEs were reported in a small proportion of patients[5, 7, 14] and no irreversible or cumulative toxic effects were noted.[5, 15]

Table 4. AEs of any Grade experienced by >10% patients (90-day safety update)

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Vomiting	[redacted]
Blood creatine phosphatase increased	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]
Dry skin	[redacted]
Pyrexia	[redacted]
Fatigue	[redacted]
Dermatitis acneiform	[redacted]
Hypoalbuminaemia	[redacted]
Headache	[redacted]
Oropharyngeal pain	[redacted]
Stomatitis	[redacted]
Pruritis	[redacted]
Abdominal pain	[redacted]
Anaemia	[redacted]
Paronychia	[redacted]
Aspartate aminotransferase increased	[redacted]
Abdominal pain upper	[redacted]
Cough	[redacted]
Rash maculo-papular	[redacted]
Constipation	[redacted]

Nasal congestion	[redacted]
Pain in extremity	[redacted]
Alanine aminotransferase increased	[redacted]
Neutrophil count decreased	[redacted]
Hypoglycaemia	[redacted]
Influenza-like illness	[redacted]
Lipase increased	[redacted]
Pain	[redacted]
Rhinitis allergic	[redacted]
Blood creatinine increase	[redacted]
Dizziness	[redacted]
Epistaxis	[redacted]
Fall	[redacted]
Haematuria	[redacted]
Otitis media	[redacted]
Decreased appetite	[redacted]
Eczema	[redacted]
Hypocalcaemia	[redacted]
Hypokalaemia	[redacted]
Lymphocyte count increased	[redacted]
Alopecia	[redacted]
Ejection fraction decreased	[redacted]
Hair colour changes	[redacted]
Hyperglycaemia	[redacted]
Proteinuria	[redacted]
Blood alkaline phosphatase increased	[redacted]
Hyperkalaemia	[redacted]
Lymphocyte count decreased	[redacted]
Upper respiratory tract infection	[redacted]
Amylase increased	[redacted]
Haemoglobin increased	[redacted]
Insomnia	[redacted]
Sinus tachycardia	[redacted]
White blood cell count decreased	[redacted]
Back pain	[redacted]
Hypernatraemia	[redacted]
Hypertension	[redacted]
Pharyngitis	[redacted]
Hyponatraemia	[redacted]
Hypophosphataemia	[redacted]
Lacrimation increased	[redacted]
Neck pain	[redacted]
Skin infection	[redacted]
Dehydration	[redacted]
Pharyngitis streptococcal	[redacted]

Urinary incontinence		[redacted]
Anxiety		[redacted]
Ear pain		[redacted]
Hypersensitivity		[redacted]
Oedema peripheral		[redacted]
Platelet count decreased		[redacted]
Rhinorrhoea		[redacted]
Sinusitis		[redacted]
Abdominal distention		[redacted]
Arthralgia		[redacted]
Cellulitis		[redacted]
Conjunctivitis		[redacted]
Hypermagnesaemia		[redacted]
Hypomagnesaemia		[redacted]
Localised oedema		[redacted]
Weight increased		[redacted]

Source: AstraZeneca Data on File (90-day safety update; tables, figures and listings).[14]

A10. Priority question. The main outcome estimated from the combined selumetinib (SPRINT) and natural history individual patient data (using propensity score matching), reported in section 9.8, is progression (defined as a ≥20% increase in tumour volume from baseline).

a) **Please justify why progression is the most important measure of effectiveness.**

b) **Please conduct an analysis of the combined selumetinib and natural history individual patient data where the outcome is PN size or PN growth (increase in size). Please estimate the effect of age on size and size difference between intervention and comparator.**

c) **Please discuss why the objective response rate, i.e. percentage of patients with complete response (CR) or confirmed partial response (cPR), was not deemed to be equally important as progression.**

a) Importance of progression as measure of effectiveness

The SPRINT Phase II Stratum I trial investigated a range of tumour volumetric measures that were all relevant in the evaluation of the clinical effectiveness of selumetinib.[2] Whilst progression-free survival (PFS) is an important measure of effectiveness (secondary outcome), other endpoints including overall response rate

(ORR; primary outcome), best objective response rate (BOR; secondary outcome) and duration of response in patients with a confirmed partial response (cPR; secondary outcome) provide a more complete picture of the treatment effect of selumetinib.

ORR, which includes complete response (CR) and cPR represents patients who experienced PN volume reductions of ≥20% from baseline. PN volume reductions of ≥20% in the absence of disease-modifying treatments are rare (see response to Question B1d).[5, 13, 16] It can therefore be confidently concluded that any responses seen in SPRINT Phase II Stratum I can be directly attributed to a treatment effect. Hence, objective response rate (ORR) is a rigorous endpoint to demonstrate the efficacy of selumetinib in the SPRINT Phase II Stratum I. The majority of children, 68% (34/50), had a cPR to selumetinib treatment, representing a ≥20% reduction in target PN volume from baseline (Gross et al. 2020; 29th March 2019 DCO).[5] Tumour size reduction of any extent is uncommon in this disease setting, demonstrating the step-change in clinical efficacy provided by selumetinib.

BOR was defined as the best response recorded from the start of treatment until progression or the last evaluable volumetric MRI assessment in the absence of progression.[2] The results for BOR provide insight into the number of patients who experienced an overall reduction in PN volume at best response, and also the number of patients who experienced disease stabilisation and an unconfirmed partial response. Whilst it was possible for patients to experience a BOR of progression, results from Gross et al. 2020 confirmed that no patients experienced a BOR of progression. In addition, 74% (37/50) of patients experienced ≥20% reduction in PN volume at BOR, 22% of patients (11/50) had a best response of stable disease and 6% of patients (3/50) had a best response of unconfirmed partial response. This is in contrast to the unpredictable and uncontrolled growth experienced by patients enrolled on the Natural History study; a 77% increase in volume from baseline was observed in the age-matched Natural History study cohort.[5, 13] The results for BOR therefore illustrate the disease stabilisation and tumour volume reduction, experienced by the vast majority of patients receiving selumetinib treatment. [5]

A durable response was defined as a cPR lasting for more than one year. This endpoint provides highly relevant evidence that the treatment effect of selumetinib is maintained over multiple treatment cycles, providing long-term benefit to patients by preventing uncontrolled tumour growth over a number of years. Of the 35 patients who had a confirmed partial response to selumetinib treatment, 28 (80%) had a durable response lasting for longer than one year, supporting the durability of treatment effect with selumetinib.[5]

PFS is an important measure of treatment effectiveness due to the impact of progression on PN-associated morbidities and patient HRQoL. Progression of PN (defined as volume increases of ≥20% compared to baseline PN volume or, an increase of ≥20% from best response if a patient had had a PR) shows a clear

association with an increase in the number and severity of PN-associated morbidities (see Section 6.1 of the company submission). In turn, increases in the number and severity of PN-associated morbidities result in deteriorating patient HRQoL.[5, 13] PFS acts as a measure of the proportion of patients who are experiencing PN volume reduction, and also those who are experiencing PN tumour control/volume stabilisation. In this setting of paediatric patients with NF1 and symptomatic, inoperable PNs, control of, or stopping, PN growth can provide a significant clinical benefit, with patients avoiding the worsening of symptoms, psychological burden and uncertainty which can result from progression.[17]. The PFS endpoint therefore acts as longitudinal measure of both disease stabilisation and tumour volume reduction, encapsulating all relevant treatment effects for patients with NF1 PN. At three years, 84% of patients in SPRINT remained progression-free, compared with 15% in the Natural History age-matched cohort.[5] Selumetinib therefore offers significant benefits to patients, through prevention of PN volume growth and therefore the prevention of disease progression.

PFS was therefore used in the propensity score analysis as it presents a longitudinal view of the efficacy of selumetinib. Furthermore, data from the Natural History study showed an ORR of 0%, making the results of a propensity score adjusted comparison a foregone conclusion.

AstraZeneca conducted additional statistical analysis of ORR using propensity score adjusted patient populations.

ORR results from the propensity score-adjusted patient populations are presented in Table 5. In all four methods, the SPRINT population demonstrated similar ORR to the original outcome from SPRINT study ([redacted] AstraZeneca CSR, 29th June 2018 DCO), in contrast with no objective response being observed in the Natural History study population. These results are aligned with the original result from the SPRINT and NH analyses, and confirm the efficacy of selumetinib in this population.

Table 5: ORR from propensity score-adjusted patient populations of SPRINT and NH studies

Propensity score adjustment method	Group	n	Number (%) of patients with response	95% CI**
1:1 match	SPRINT	37	[redacted]	[redacted]
	NH	37	[redacted]	[redacted]
1:2 match	SPRINT	46	[redacted]	[redacted]
	NH	43	[redacted]	[redacted]
IPTW	SPRINT	129.1*	[redacted]	[redacted]
	NH	122.1*	[redacted]	[redacted]
Stabilised IPTW	SPRINT	51.6*	[redacted]	[redacted]
	NH	73.3*	[redacted]	[redacted]

* Sum of weights from propensity score
** The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
Abbreviations: CI: confidence interval; IPTW: Inverse Probability of Treatment Weighting; NH: Natural History; PN: plexiform neurofibroma.
Source: AstraZeneca Data on File. Further information available upon request.

b) Analysis of the combined SPRINT and Natural History data with PN size/growth as outcome

When the annual growth rates of target PN in the SPRINT Phase II Stratum I and Natural History study populations are compared, using four different propensity score adjustment methods, patients treated with selumetinib consistently show negative growth rates (i.e. PN volume reduction) while the Natural History study patients show positive growth rates (i.e. PN volume increase).

The results of this analysis are shown in Table 6 (percentage change in volume) and Table 7 (absolute change in volume). The adjusted mean difference was consistent across all four methods (range in percentage change, −35.3% to −38.6%; range in absolute change, −174.1ml to −195.9ml), thereby clearly demonstrating the substantial efficacy of selumetinib in reducing the volume of target PN. Further information on the results of these analyses is available on request.

The effect of age on PN size and size difference is discussed within the response to Question B2c.

Table 6. Percentage change in target PN volume (mean difference by propensity score adjustment method) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Propensity score adjustment method	Group	n	Time period, years, Mean (95% CI)	PN volume % change/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1:1 match	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
1:2 match	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
IPTW	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]

	Adjusted mean difference		
Stabilised IPTW	SPRINT		
	NH		
	Adjusted mean difference		

Abbreviations: CI: confidence interval; IPTW: Inverse Probability of Treatment Weighting; NH: Natural History; PN: plexiform neurofibroma.
Source: AstraZeneca Data on File. Further information available upon request.

Table 7. Absolute change in target PN volume (mean difference by propensity score adjustment method) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Propensity score adjustment method	Group	n	Time period, years, Mean (95% CI)	PN volume change(ml)/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1:1 match	SPRINT				
	NH				
	Adjusted mean difference				
1:2 match	SPRINT				
	NH				
	Adjusted mean difference				
IPTW	SPRINT				
	NH				
	Adjusted mean difference				
Stabilised IPTW	SPRINT				
	NH				
	Adjusted mean difference				

Abbreviations: CI: confidence interval; IPTW: Inverse Probability of Treatment Weighting; NC: not calculable; NH: Natural History; PN: plexiform neurofibroma.
Source: AstraZeneca Data on File. Further information available upon request.

c) Importance of ORR

As detailed in the response to Question 10a, whilst ORR constitutes a rigorous endpoint to demonstrate the efficacy of selumetinib in the SPRINT Phase II Stratum I, PFS was used preferentially for the propensity score analysis as it represents a

more longitudinal measure of both disease stabilisation and tumour volume reduction, encapsulating all relevant treatment effects for patients with NF1 PN (please refer to the response to Question A10a for further details).

A11. Priority question. The CS mentioned a naïve comparison between SPRINT Phase II Stratum I and age-matched cohort from the NCI Natural History Study and another naïve comparison of PFS tipifarnib Study 01-C-0222.

a) **Please highlight to the ERG the relevant section(s) of the SPRINT study CSR which specifies the planned external comparison between SPRINT Phase II Stratum I and age-matched cohort from the NCI Natural History Study.**

b) **Please provide details how the two studies used for external comparison were identified.**

c) **Please provide details if there are other studies which could be used for comparison. Please comment if SLR was considered for this and justify your response.**

d) **Please justify the statement regarding tipifarnib study: *"The placebo arm of tipifarnib Study 01-C-0222 was designed in such a way that it could be used as an external control for other trials in this indication and has been used as a historic control for other clinical trials, making it highly suitable for use as a comparator for SPRINT Phase II Stratum I data"*. Please provide the references for the studies in which the control arm was used as a historic control.**

a) Evidence for planned external comparison

Details of the planned comparison of SPRINT Phase II Stratum I to an age-matched cohort from the National Cancer Institute (NCI) Natural History study, as an external comparator, can be found in Section 4.3 (page 76) of the pre-specified Statistical Analysis Plan.[18]

b and c) Identification of studies for comparison

A prior SLR by Copley-Merriman et al., published in 2021,[19] was conducted to identify studies reporting on the natural history, disease burden, and treatment patterns among patients diagnosed with NF1 and PN. Of the studies investigating PN growth, the review identified two publications analysing data from the NCI

Natural History study (including Gross et al. 2018[13]), in addition to two further natural history studies from Germany, and a final study which pooled data from a number of interventional trials and a natural history study.

Whilst the searches for this SLR were performed in May 2019, targeted searches of Medline via PubMed for 'neurofibromatosis type 1' AND 'plexiform neurofibroma' AND 'growth', limited to the last three years (up to September 2021), do not identify any new, relevant natural history studies (beyond one additional analysis of the NCI study [Akshintala et al. 2020][16], known to AstraZeneca and referenced in the submission document). With the rarity of NF1 PN, and the slow rate of development of research in this disease area, it is incredibly unlikely that data from any relevant natural history studies would have been published, that AstraZeneca would be unaware of.

Of all the natural history studies identified in the Copley-Merriman SLR, the NCI Natural History study was most aligned to SPRINT Phase II Stratum I in terms of the method used to assess PN volume (volumetric MRI) and median age of patients, and provided the most extensive range of data.[19] In addition, the NCI Natural History study is the most comprehensive NF1 PN natural history study of those identified, providing a comprehensive description of the disease course in a relatively large patient cohort.[5] A further consideration was that the NCI Natural History study and tipifarnib Study 01-C-0222 were both carried out by the same group, the NCI Paediatric Oncology Branch (POB), which has been performing research into NF1 PN treatment for more than 10 years, unlike the other two natural history studies identified in the SLR. This is the same group which carried out SPRINT Phase II Stratum I and so the methodologies used are highly similar and comparable between studies. For example, the assessment of PN volume via MRI scan reading was conducted by the same NCI reader for all three studies. The NCI Natural History study and tipifarnib Study 01-C-0222 were therefore considered the most appropriate external control for SPRINT Phase II Stratum I.

d) Tipifarnib control arm as a historical control

As stated by Widemann et al. (2014), "the placebo arm of the tipifarnib Study 01-C-0222 was designed to be used as a historical control group for Phase II trials of other drugs in the NF1 PN indication".[20] Studies intending to use this control group as an external historical control are required to use the same eligibility criteria as Study 01-C-0222. This includes requiring participants to have evidence of PN growth before study entry and the participant pool having a similar age range to patients in the tipifarnib study, to ensure comparisons are valid.

The comparison between SPRINT Phase II Stratum I and the tipifarnib Study 01-C-0222 placebo arm was suitable, as the comparison was carried out using only the SPRINT patients who had progressive disease at enrolment, aligning with the Study

01-C-0222 enrolment criteria. In addition, the two studies had very similar eligibility criteria.[5, 7, 20]

The control arm of the tipifarnib Study 01-C-0222 has also been used as an external control for the following studies:

- Widemann et al. 2014:[21] Phase II trial of pirfenidone in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas
- Weiss et al. 2014:[22] Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: a Neurofibromatosis Clinical Trials Consortium phase II study
- Jakacki et al. 2017:[23] Phase II trial of pegylated interferon alfa-2b in young patients with neurofibromatosis type 1 and unresectable plexiform neurofibromas

A12. Priority question. Section 9.8 of the CS describes a propensity score analysis of SPRINT Phase II Stratum I and the Natural History studies. This analysis was conducted to *"to understand the potential impact of adjusting for baseline covariates across the study populations on estimates of treatment effect"*.

However, it appears as if some potentially relevant baseline characteristics, e.g. target PN status or time from diagnosis of NF1 and PN, respectively, could not be accounted for as these were not reported in the Natural History studies (e.g. Table C10).

Please discuss the potential impact on the comparability and the analyses of these studies.

It is expected that including baseline characteristics not reported in the Natural History study would have an negligible overall impact on the results, due to the following considerations:

- Following matching/weighting, all included baseline characteristics were similar across SPRINT Phase II Stratum I and the Natural History study, as demonstrated by reduced standardised differences <0.2; it is therefore reasonable to assume that this would also be the case for any further unreported baseline characteristics
- Further to this, it can reasonably be expected that even before matching there would be no substantial variation across the baseline disease characteristics that

have not been accounted for, such as time from diagnosis and target PN status, between the two study populations; for example:

  - Both studies were carried out by the NCI and used the National Institutes of Health Clinical Centre in Maryland, USA as a trial site; it can therefore be expected that time to diagnosis would be generally comparable between the two patient cohorts

  - Neither study applied restrictions with regards to target PN status during the enrolment of patients (i.e. patients with progressive PN as well as patients with stable PN were enrolled for either study); as such it can be expected that the proportions of progressive/non-progressive PN, whilst naturally variable, would be broadly similar for both studies

- The results of the analysis were highly robust and consistent across the four different methods that were applied; it is therefore reasonable to assume that the overall results of the analysis, demonstrating a strongly reduced risk of progression with selumetinib, would remain largely the same following the hypothetical inclusion of additional baseline characteristics

A13. Table A3 presents the dosing scheme for selumetinib 25 mg/m^2 BID while Table A4 shows the selumetinib doses per phase and stratum in the SPRINT trial.

Please elaborate how these Tables relate, i.e. how the dosing scheme described in Table A3 was applied in the SPRINT trial.

For the dose-escalation SPRINT Phase I study, a dosing range of 20–30 mg/m^2 BSA BID was explored to determine the maximum tolerated dose of selumetinib; the results of this study indicated that patients were able to receive selumetinib on a long-term basis with a maximum tolerated dose of 25 mg/m^2 BSA BID.

Subsequently, for both Stratum I and Stratum II of SPRINT Phase II selumetinib was administered with a dose of 25 mg/m^2 BSA twice daily (BID; as detailed in Table A3 of the submission document).

Please also refer to the response to Question B14a for further details on selumetinib dosing (and corresponding selumetinib treatment costs).

A14. Please provide information if the data of the patients offered selumetinib as part of Early Access Program in England are available to the company. If yes, please provide the data.

We can confirm that no data from the patients currently receiving selumetinib as part of the Early Access Program in England will be available to the company in time to support this submission.

A15. Table C3 provides details of relevant published studies. Please comment, for each study, the reason why it was not included in the main body of the CS referring to the NICE scope.

Table 8 provides an overview of all published studies included in the clinical SLR, due to meeting the pre-defined inclusion criteria, as well as their relevance to the decision problem. Please note that, even though these studies were not included in the main body of the submission, the respective results are generally aligned with the evidence presented for SPRINT Phase II Stratum I.

Table 8. Relevance of included published studies to the decision problem

Primary study reference	Relevance to the decision problem
Baldo 2020[24]	Not considered relevant due to presenting results of a small case series (N=9), with unclear robustness/precision of the reported results (see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).
Coyne 2019[25]	Not considered relevant due to presenting results for adult (≥18 years of age) patients with NF1 PN only.
Dombi 2016[26]	Not considered relevant to the decision problem due to presenting the results of a dose-escalation phase 1 study (SPRINT Phase I).
Espirito Santo 2020[27]	Not considered relevant due to presenting only categorical results of a small case series (N=19; see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).
Glassberg 2020a[28]	Not considered relevant due to presenting results of Stratum II of the SPRINT Phase II study, which falls outside of the licensed indication of selumetinib (by including patients with NF1 PN *which have the potential to become symptomatic*).
Gross 2020[5]	Considered to be relevant to the decision problem by presenting results of SPRINT Phase II Stratum I, which also supported the marketing authorisation for selumetinib in the relevant indication.
Kudek 2019[29]	Not considered relevant due to presenting only limited results of an ongoing small case study (N=3; see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).
Passos 2020[30]	Not considered relevant due to presenting only limited results of a single case study (N=1; see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).

Abbreviations: NF1: type 1 neurofibromatosis; PN: plexiform neurofibroma.

A16. Section 9.4.1 states that the placebo arm was not feasible due to reasons listed in the CS. Tipifarnib Study 01-C-0222 was randomised, cross-over, double-blind, placebo-controlled trial in patients with clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity. Please comment if similar design was considered for the study of selumetinib and justify your response.

Selumetinib is a MEK inhibitor, a class of treatments which have a well-defined and equally well-described adverse event profile (including skin and gastrointestinal adverse events). Maintaining blinding versus placebo for a sufficient duration during a clinical trial of a MEK inhibitor is therefore challenging.

The tipifarnib Study 01-C-0222 and SPRINT Phase II trial were both designed and run by the NCI POB. As stated by Widemann et al. (2014), “the placebo arm of the tipifarnib Study 01-C-0222 was designed to be used as a historical control group for Phase II trials of other drugs in the NF1 PN indication” (please refer to the response to Question A11 for further details).[20] This reduced the necessity for other interventional trials to include a placebo arm, for both practical and ethical reasons; as such, the SPRINT Phase II study was designed to be a single arm study to be compared against the available historical control, and other appropriate available control data.

During 2018 and 2019, the topic of placebo designs has been discussed with NF physicians and NF patient organisations in the European Union. Neither group were supportive of exposing their paediatric patients to a placebo treatment, supporting the decision to not use a placebo arm in the SPRINT Phase II trial. As per the eligibility criteria for the SPRINT Phase II trial, enrolled patients have tumours (PN) which can cause considerable symptoms and morbidity. For example, in SPRINT Phase II Stratum I, [redacted] of the study population ([redacted]) were experiencing PN-associated pain on enrolment.[7] The patients enrolled in SPRINT Phase II Stratum I had symptomatic inoperable PN, and therefore had no pharmacological, disease modifying treatments available to them, and would not have been eligible for surgical treatment.[2] The patients therefore had a great need for an effective pharmacological treatment, and it would have been unethical for them to have received placebo treatment. In light of the significant unmet need facing these patients, if a placebo arm had been included, it would have been likely that there would have been significant attrition of placebo patients from the trial, who would have discontinued to seek active selumetinib treatment instead.

In addition, as the tipifarnib Study 01-C-0222 was a placebo controlled study design, it took 4.5 years to enrol 62 patients across 10 sites.[20] If the same had been attempted for selumetinib (with a target enrolment of 62 patients), it would have been likely to also take around 4.5 years to enrol the patients; in addition, a minimum of two years on treatment would be required before data lock. Hence, in all likelihood it would have taken at least seven years to obtain the results from the trial. This delay

in the availability of data, and the opportunities that this evidence of clinical efficacy would provide with regards to allowing patients access to an effective pharmacological treatment option, would have to be considered unethical. In addition, a less comprehensive range of clinical outcome assessments was performed for the tipifarnib study, when compared with SPRINT Phase II Stratum I, and a similar limitation would likely have been forced on the SPRINT trial design if a placebo arm had been included.

A17. Table C16 in section 9.6.1 of the CS provides the summary of tumour volumetric results. Based on the Table C5 of the CS, overall response rate (ORR) to selumetinib was *"defined as the rate of confirmed PR and CR (PR defined as PN decrease ≥20% compared to baseline; CR defined as the disappearance of the target PN) using centrally read volumetric MRI"*. However, the NICE scope listed CR and PR rate as separate outcomes.

Please provide the details for complete response (CR) and partial response (PR) separately.

An ORR of 68% was observed in SPRINT Phase II Stratum I at DCO 29th March 2019 (Gross et al. 2020). This ORR represents the 34 patients (68%) who experienced a confirmed partial response; a further three patients (6%) experienced an unconfirmed partial response. A total of 37/50 patients (74%; 95% CI, 60 to 85) therefore had a partial response. No patients experienced a complete response.[5]

The ORR had not changed by DCO 27th February 2021.[6] The median best tumour response was very similar at the two most recent DCOs: −27.9 at the 29th March 2019 and −27.2% at the 27th February 2021.[5, 6]

A18. Section 9.6 of the CS report on clinically meaningful improvements for HRQoL (PedsQL), PN-associated pain, airway function (R5) and motor function (the patient-related mobility and the upper extremity scores). However, the thresholds for clinically meaningful differences were not provided. Please provide the thresholds along with supporting references.

Clinically meaningful thresholds (as used in the primary analysis of SPRINT Phase II Stratum I) for the requested outcome assessments are provided together with supporting references in Table 9.

Clinically meaningful thresholds were primarily determined by using both distribution-based (based on one-half standard deviation of the respective study baseline scores) or anchor-based (based on the global impression of change as anchor) approaches; where possible for selected assessments, data from published literature were used to define the clinically meaningful threshold.[7]

Table 9. Clinically meaningful thresholds for selected outcome assessments

Clinical outcome assessment	Clinically meaningful threshold (primary analysis)	Supporting reference
HRQoL (PedsQL total score)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores.[a] • Self-reported: [redacted] • Parent-reported: [redacted]	AstraZeneca Data on File (SRINT CSR)[7]
PN-associated pain (NRS-11)	A decrease of two points on the NRS-11 was considered clinically meaningful based on several studies in other populations.	AstraZeneca Data on File (SPRINT SAP)[18] Farrar et al. 2000[31] Kendrick et al. 2005[32] Salaffi et al. 2004[33] Voepel-Lewis et al. 2011[34]
PN-associated pain (PII)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores. • Self-reported: [redacted] • Parent-reported: [redacted]	AstraZeneca Data on File (SRINT CSR)[7]
Motor function (PROMIS mobility)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores. • Self-reported: [redacted] (raw score); [redacted] (transformed) • Parent-reported: [redacted] (raw score); [redacted] (transformed)	AstraZeneca Data on File (SRINT CSR)[7]
Motor function (PROMIS upper extremity)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores. • Self-reported: [redacted] (raw score); [redacted] (transformed) • Parent-reported: [redacted] (raw score); [redacted] (transformed)	AstraZeneca Data on File (SRINT CSR)[7]

Airway function (R_5)	Any change of ≥20% from baseline was considered clinically meaningful, with a decrease in resistance indicating improvement and an increase in resistance indicating worsening.[b] Otherwise, it was concluded that no change had occurred. These response criteria are recommended by the REiNS functional group.	AstraZeneca Data on File (SPRINT SAP)[18] Plotkin et al. 2016[35]

[a] In addition to the use of distribution-based clinically meaningful thresholds for the primary assessment of HRQoL, patients were also classified with impaired global HRQoL (Yes/No) at each pre-cycle visit, using linearly transformed PedsQL scores; patients were classified with impaired global HRQoL if their total or domain scores fell one standard deviation below the population sample mean as reported by Varni et al 2003.[36] [b] No patients enrolled in this study had a baseline score on the Apnoea-Hypopnoea Index (AHI) of >5, considered to be the lower limit necessary to see a meaningful effect of treatment.
Abbreviations: CSR: clinical study report; HRQoL: health-related quality of life; NRS-11: Numerical Rating Scale 11; PedsQL: Paediatric Quality of Life Inventory; PII: Pain Interference Index; PROMIS: Patient-Reported Outcomes Measurement Information System; R5: resistance at 5Hz; REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis ; SAP: statistical analysis plan.

Section B: Clarification on cost-effectiveness data

Model structure and implementation

B1. Priority question. The ERG has concerns regarding the validity of the current model structure. The model structure (e.g. Figure D2) seems to be incorrect and favours the intervention (selumetinib). Detailed comments are given below:

a) **Patients in both the intervention and comparator arms should enter the model in the same health state(s). At baseline (beginning of the simulation), patients should be the same regardless of the treatment arm, because treatment has not started yet. In the model, however, all patients in the selumetinib arm start in the PFS health state (even though Table C10 shows that in SPRINT there are progressive patients at baseline) and all patients in the comparator arm start in the PD health state. This implies that 1) selumetinib and the comparator are assessed in different patient populations, and 2) the model is biased in favour of selumetinib.**

b) **Page 38 of the CS states that in the Natural History study, 49/57 (86%) participants with PN underwent a ≥20% increase in tumour volume**

between baseline and maximum assessment (median time between baseline and maximum assessment was 6.5 years). This implies that 14% of patients in the Natural History study have not progressed at the time of the maximum assessment. However, in the model all patients in the comparator arm start in progression. This implies that the model is biased in favour of selumetinib.

c) **The previous point is supported by the following: on page 94 of the CS, it is explained that children in the SPRINT trial had a higher probability of PFS over 3 years compared to the Natural History study age-matched cohort (84% vs 15%), [redacted] (89% vs 21%). Thus, even in the Natural History study age-matched cohort, there are patients in PFS. The same is also suggested by Table C17 and Figure C5. This supports the assumption that PFS should also be in the comparator arm of the model.**

d) **Further, on page 39 it is mentioned that in the Natural History study, 9% of patients experienced a spontaneous tumour volume reduction over the full follow-up period ([redacted] years). Even if 9% is deemed a small proportion (certainly not irrelevant), it shows that patients in the Natural History are allowed to move from progression to the PFS health state. However, in the economic model, patients are not allowed to transition from progression to the PFS health state. It is unclear the direction of the bias in this case, since it is expected that patients who have progressed in the selumetinib arm could also experience spontaneous tumour volume reduction. Nevertheless, a full Markov model would be needed to allow patients to transition from progression to PFS.**

e) **Based on the points above, please adjust the model so that the following changes are included: 1) add a PFS health state in the comparator arm [note this also requires the estimation of PFS for the comparator arm], 2) the initial distribution of patients per health state is the same in the intervention and the comparator arms [note this requires estimates for the initial distribution of patients per health state, which**

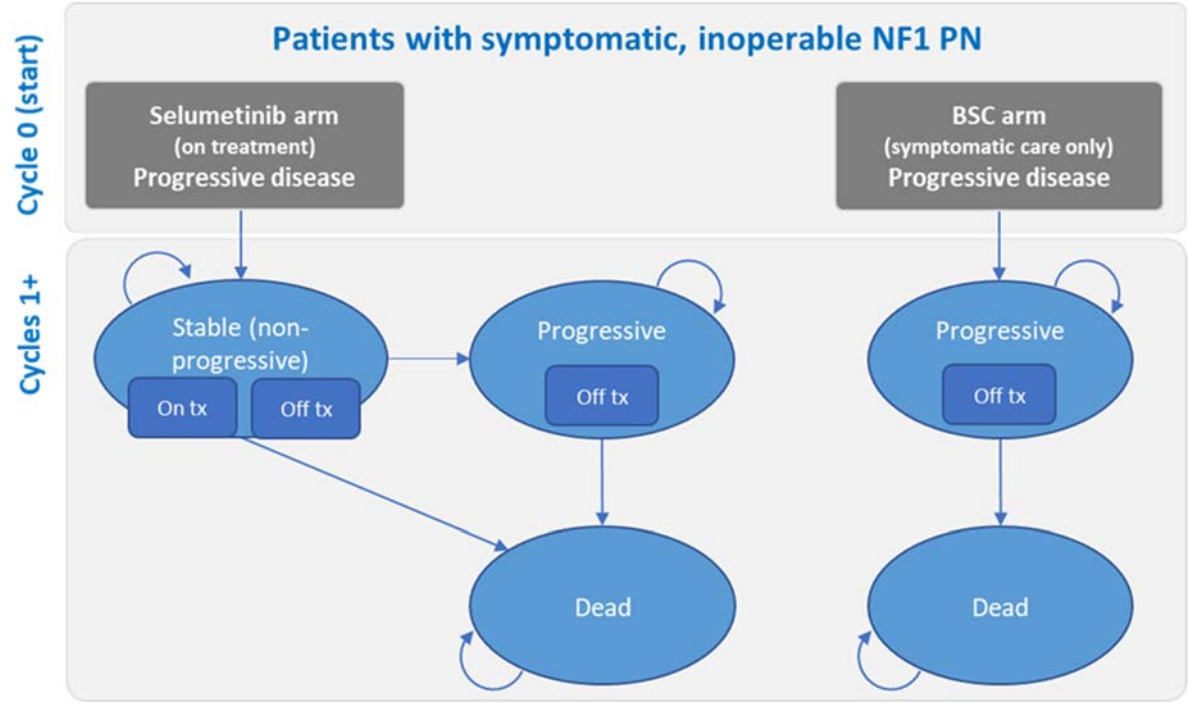
could be done for example by using Table C10] and 3) include transitions from PD to PFS in both treatment arms.

a) Patient populations entering the model

The description of the model was unclear and the original model schematic was incorrect as all patients start in the same progressive disease state.

The model assumes that all patients enter the model in a progressive disease health state and the diagram has been revised to make this clearer (Figure 2). As noted in Section 12.1.3 of the submission, "patients [receiving selumetinib] experience disease stabilisation within the first year of treatment and remain in the progression-free state until disease progression, which is modelled based on the PFS data from SPRINT Phase II Stratum I".[5]

Figure 2. Revised model schematic



In the model, this progressive state is essentially associated with a baseline utility value for a patient with a symptomatic, inoperable PN that impacts their HRQoL. The model assumes that patients who receive selumetinib will experience some improvement in HRQoL (as demonstrated by the mean improvement in PedsQL seen in SPRINT Phase II Stratum).[7] For the purposes of the model, this improvement is defined as stable (non-progressive) disease and patients have an improved HRQoL. A proportion of patients receiving selumetinib may return to the progressive disease state; the PN volume for these patients increases by ≥20% compared with baseline or, an increase of ≥20% from best response if a patient had had a PR and their associated HRQoL tends back to the baseline value.

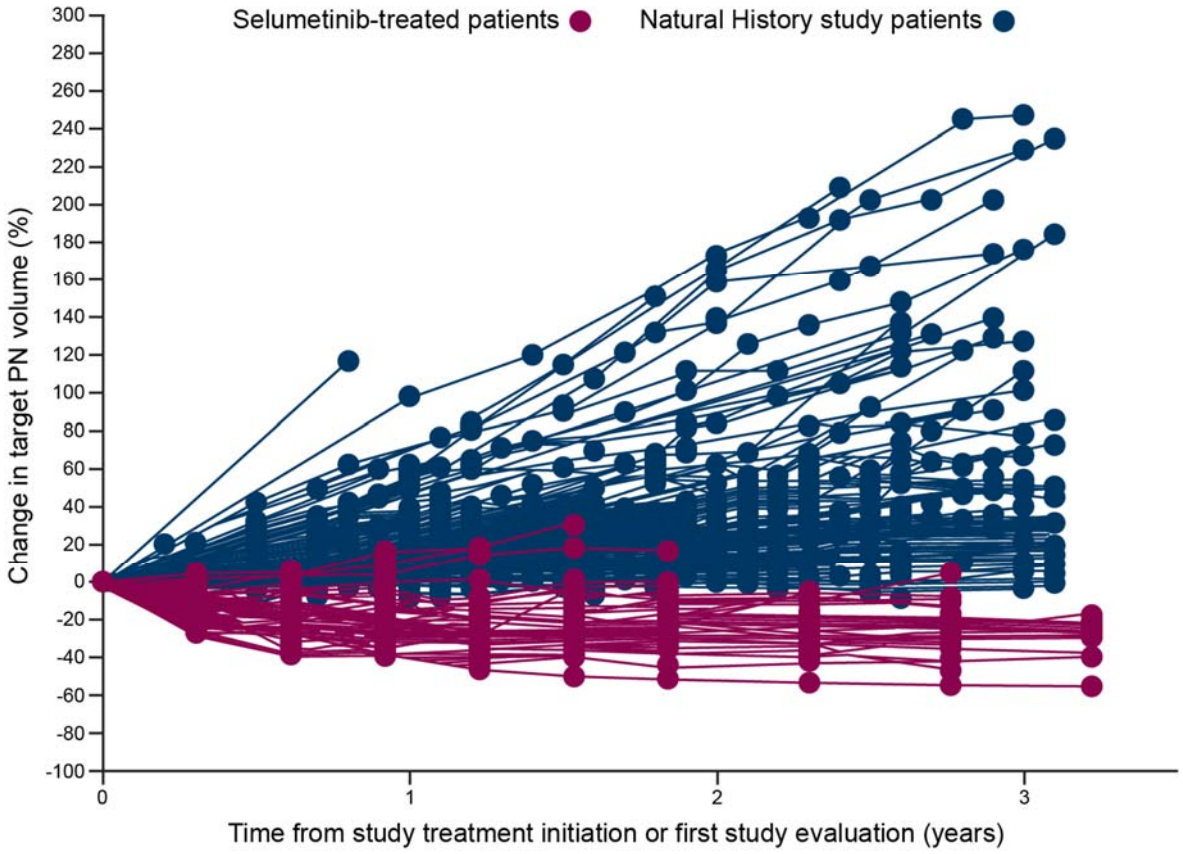
For patients receiving BSC, there is no active treatment to reduce the PN volume and even though a small proportion of patients may experience some spontaneous reduction at some point in their lifetime, as noted in the subsequent response below, this is not equivalent to a partial response or response as defined in SPRINT, especially in paediatric patients. As such, patients in the BSC arm are assumed to stay in the 'progressive' health state and receive the age-adjusted baseline HRQoL for the duration of the analysis. This can be considered a conservative assumption as the Natural History study data suggest that the vast majority of patients will continue to experience increases in PN volume until adulthood. These PN volume increases can correspondingly increase the number and severity of PN-associated morbidities and likely worsen patient HRQoL, as described in the response to Question A10a (please also refer to the response to Question B10c).

b) Progression in the comparator arm

In the model, the same cohort of patients are considered in each arm (as detailed in the revised model diagram in Figure 2) and enter the model with the same health state distribution (i.e. all patients are in a progressive state); there is therefore no bias in favour of selumetinib.

In addition, Figure 3 and Figure 4 demonstrate that most of the patients in the Natural History study experienced tumour volume increases from baseline. Within the model, it is assumed that, for those patients on BSC, the HRQoL will remain constant for the duration of the analysis (excluding the adjustment for age using the Ara and Brazier algorithm). If it is assumed that the 14% of patients in the BSC arm do not progress, the remaining 86% of patients are likely to have experienced ≥20% tumour volume increase from baseline and therefore may have a lower utility score than the baseline.[5] Although the current model does not consider this specifically, we feel the exclusion is conservative and will favour BSC.

Figure 3. Percentage change in target PN volume during selumetinib treatment in SPRINT Phase II Stratum I compared to an age-matched Natural History study control cohort



Abbreviations: PN: plexiform neurofibromas.
Source: Gross et al. 2020.[5]

Figure 4. Change in PN growth from individual patient profiles, over 5 years by age group

[redacted]

Source: AstraZeneca Data on File.[37]

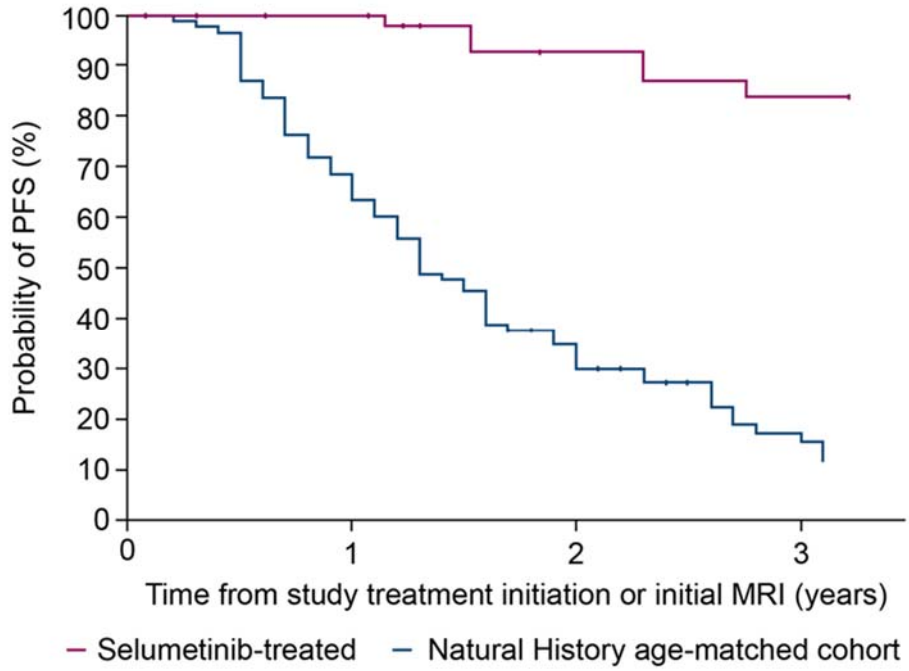
c) Progression in the comparator arm

In the SPRINT study, progression was defined as a PN volume increase of ≥20% compared with baseline or, an increase of ≥20% from best response if a patient had had a PR.[2] Figure 5 illustrates that 16% of patients receiving selumetinib had progressed and that 85% of patients in the Natural History study had progressed further than at the point of study entry. This does not mean that 15% of the Natural

History study patients had not experienced any PN volume growth, just that these 15% of patients had not experienced a PN volume increase of ≥20%. Indeed, as shown in Figure 3, most patients still have some degree of tumour growth. As such, it is appropriate that all patients in the BSC arm are considered to have the baseline utility associated with a progressed state.

By assigning a constant utility to patients in the progressed state the model likely also underestimates the benefit of selumetinib as it is likely that HRQoL would decline with the increasing PN volume of patients in the progressed health state, the state where BSC patients reside within the model.

Figure 5. PFS during selumetinib treatment in SPRINT Phase II Stratum I compared to the age-matched Natural History study control cohort



Abbreviations: MRI: magnetic resonance imaging; PFS: progression-free survival.
Source: Gross et al. 2020.[5]

d) Tumour volume reduction

As stated in Section 6.1 of the submission, Akshintala et al. 2020 reported a spontaneous reduction in PN volume of a few patients (10/113, 8.8%) included in the Natural history study.[16]

However, spontaneous tumour volume decreases were defined as a final volume at follow up that was ≥10% lower than the maximum volume, with decrease documented on at least two successive MRI scans in patients not undergoing PN-directed medical therapy during this time period. The interval between 2 scans in this study ranged between 3 months to 3 years. The observed reduction in volume for these 10 patients was observed over many years ranging between 3.7–10.3 years.

Seven of these 10 patients were already in their adulthood (18.2–30.6 years old) when their maximal volume was recorded.[16] This is contrast to the stricter and shorter criterion in SPRINT Phase II Stratum I, where definition of partial response is decrease in the volume of the target PN by 20% or more compared with the baseline, and must be observed within 3 to 6 months for confirmation.[2] For example, in a case reported in Figure 4 of Akshintala et al. 2020, the patient experienced tumour volume reduction from the maximum size but this was still a ≥20% increase from baseline and defined as *progressive* disease by the definition used in the SPRINT trial.[16]

Akshintala et al. further note that none of the spontaneous volume shrinkage were a ≥20% decrease, concluding that a 20% change could signify a treatment effect in children and young adults with NF1.[16]

We therefore feel that while there may be a degree of spontaneous PN volume reduction that has been observed with patients reaching adulthood, this is not sufficient to be considered equivalent to the treatment response observed in SPRINT trial and as such it would be inappropriate to include in the current analysis.

e) Appropriateness of the model

We believe that the model structure is appropriate to the decision problem and reflects the key clinical benefits of selumetinib.

Whilst a small proportion of patients in the control arm of the model may experience some spontaneous PN volume reduction, there is no evidence to support that this is a clinically relevant reduction, or equivalent to the 20% volume decrease from baseline required to achieve partial response. As such, no modifications to the model structure have been conducted to address this question.

As noted in response to Question B1a, patients enter the model in a progressive disease state with a baseline utility. Those receiving BSC do not improve, and maintain this baseline HRQoL for the duration of the analysis. This is despite the Natural History data indicating that the majority of patients will experience a ≥20% PN volume increase and therefore may have lower utility score than the baseline utility value. Although the current model does not consider this specifically, we feel the exclusion is conservative and will favour BSC.

B2. Priority question. The company indicated that due to limited availability of data, other model structures were deemed unfeasible, and a simplified area under the curve (AUC) model structure was deemed most appropriate to model the disease course of NF1 PN and capture the HRQoL outcomes for patients with and without selumetinib.

The ERG has concerns regarding the validity of this statement. Throughout the CS, the heterogeneity of NF1 and PN is emphasised. The evidence provided also suggests that disease progression strongly varies with age. For example, "*PN growth rates are most rapid in children with NF1 PN, with patients aged 3–5 years experiencing unpredictable and uncontrolled PN growth at a median growth rate of 35% per year*". Also, "*as patients age, PN growth rates tend to slow and tumour volumes plateau into adulthood*". This strongly suggests age-dependent transitions. Please answer the following questions:

a) **The ERG considers that a patient-level model would be the most appropriate to capture disease heterogeneity. Please explain why a patient-level model was deemed unfeasible.**

b) **Because AUC models are not the most appropriate to capture heterogeneity, please explain what limitations in the available data justified the choice of the AUC model structure.**

c) **Please provide 1) the average PN growth rate for the different age categories shown in Figure B3 and 2) the average PN growth rate for all patients (across all age categories).**

d) **Please clarify whether the model assumes that the average PN growth rate (across all age categories) is applied to patients in the model (starting at 10 years old – almost at the age PN growth rate starts to plateau in the current evidence).**

e) **Please quantify the difference between the average PN growth rate for a 10-year-old patient and the average PN growth rate across all years.**

f) **Please explain whether 1) the association between age and disease progression (PN growth rate) is captured in the current model, 2) age is expected to be a treatment effect modifier and 3) PN volume and number of PN-related morbidities are expected to be treatment effect modifiers.**

g) **If any of the associations mentioned in the previous point are deemed relevant, please include them in the model.**

a) Patient-level model

A patient level model was not feasible due to insufficient data.

During the original model scoping, a regression-based patient-level model was considered with the intention of including PN location, baseline PN volume, PN growth rates, and age as potential covariates. However, the only data available to inform this were the IPD from SPRINT Phase II Stratum I; as these were limited to 50 patients, no robust statistical analysis could be performed. In addition, unfortunately no patient-level HRQoL data were available from the Natural History study to support such analysis; this also meant that no treatment effect could be determined for selumetinib. Similarly, when assessing these tumour volumetric outcomes in relation to PedsQL data, given the limited availability of data, no robust association with any of these parameters and HRQoL could be identified. Therefore, modelling PN location, PN volume, PN growth rate etc, would not have informed any HRQoL estimates for the model.

To provide some context, of the 50 patients in SPRINT Phase II Stratum I, the median age was [redacted] years (range, [redacted]) and the median target PN volume at baseline was [redacted].[7] The distribution of patient age at baseline is shown in Figure 6, illustrating the small number of patients in any banding.

Figure 6. Distribution of SPRINT patient age at baseline

Intuitively, it was hypothesised that there would be an association between PN location, volume and the symptoms experienced, but subgrouping the analysis by PN location would have reduced the maximum sample size to 12 patients (see Table 10). As such, combined with the other covariates, there is an insufficient number of patients to power any meaningful subgrouping analysis. As such, rather than

creating a complex model that would require a substantial number of assumptions with a high degree of uncertainty, a more pragmatic approach was developed that focused on a limited number of broader assumptions. This pragmatic is approach is in keeping with the NICE HST programme which recognises the data challenges associated with rare diseases.

Table 10. Target PN locations

Location of target PN	Patients, n (%) N=50
Neck and trunk	[redacted]
Trunk and limbs	[redacted]
Head only	[redacted]
Head and neck	[redacted]
Trunk only	[redacted]
Limbs only	[redacted]

Source: AstraZeneca Data on File (SRINT CSR).[7]

b) AUC model structure

As discussed in response to Question B2a, alternative model structures were explored but were not feasible due to insufficient data. The AUC model structure, which is widely used across NICE technology appraisals, enables a robust and appropriate analysis to be conducted, whilst minimising the number of assumptions required compared with more complex model structures. This pragmatic approach therefore best utilises the available data by focusing on a limited number of broader assumptions, and provides a reliable estimate of the cost-effectiveness of selumetinib.

c) Average PN growth rate

The average PN growth rates for the different age categories of Natural History study patients are presented in Figure B3 of the company submission, and Figure 7 below. Comparisons of PN growth rates between the SPRINT Phase II Stratum I and Natural History study populations for the same age categories are summarised in Table 11 (*percentage* change in target PN volume) and Table 12 (*absolute* change in target PN volume). Further information on the results of these analyses is available on request.

Figure 7. Change in PN growth from NCI Natural History study individual patient profiles, over five years by age group

[redacted]

Source: AstraZeneca Data on File.[37]
Abbreviations: PN: plexiform neurofibroma.

In all age categories, patients treated with selumetinib experienced tumour volume reduction, while the Natural History study population experienced tumour growth. The PN volume reduction per year with selumetinib treatment was relatively similar in different age groups, except for the age group aged ≥16 years, where growth rates generally being to plateau in the Natural History study group. However, the number of patients aged ≥16 was very small in both arms, and as such it is difficult to make a robust comparison in this age category.

The adjusted mean difference was larger across the younger age groups, reflected by the PN volume change/year in the NH group becoming smaller as patients get older. However, despite this natural change in growth rate, there still are big differences between the two treatment arms, even in older patients (see tables below), thus confirming the efficacy of selumetinib across all licensed age groups.

Table 11. Percent change in target PN volume (mean difference by age category) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Age category	Group	n	Time period, years, Mean (95% CI)	PN volume % change/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1-<7	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
7≤12	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
12≤16	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]

≥16	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
All age	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]

Abbreviations: CI: confidence interval; NC: not calculable; NH: Natural History; PN: plexiform neurofibroma.
Source: AstraZeneca Data on File. Further information available upon request.

Table 12. Absolute change in target PN volume (mean difference by age category) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Age category	Group	n	Time period, years, Mean (95% CI)	PN volume change(ml)/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1≤7	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
7≤12	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
12≤16	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
≥16	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
All age	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]

	Adjusted mean difference		[redacted]

Abbreviations: CI: confidence interval; NC: not calculable; NH: Natural History; PN: plexiform neurofibroma.
Source: AstraZeneca Data on File. Further information available upon request.

d) Average PN growth rate clarification

The model does not directly consider PN growth rate; however, as noted in response to Question B1, patients who receive selumetinib are assumed to achieve a progression-free state within a year and remain there unless they progress. In patients who receive selumetinib and subsequently progress, the HRQoL is assumed to move linearly back to the baseline HRQoL. This is assumed to occur over a 5-year time horizon and therefore, by inference, if the decrement in HRQoL is occurring due to increased PN growth the model assumes that this rate of growth is the same across all ages.

Patients receiving BSC remain in the 'progressive' untreated health state and receive the baseline HRQoL. This can be considered conservative as patients in this treatment group are likely to experience an increase in PN volume, which is also likely to further reduce the HRQoL. Further to this, whilst in older paediatric patients PN growth rate may slow, these patients will still have high disease burden due to accumulated tumour growth and morbidities. However, as noted above, statistical power is insufficient to support this inference, which has led to the simple treated/untreated utility dichotomy implemented in the model.

e) Average growth rate quantification

The relative size of the 10-year old cohort ([redacted]) is too small to provide a representative growth rate. As noted above, the PN growth rate is not directly considered with the current modelling approach.

f) Treatment effect modifiers

The current model does not consider any association between age, disease progression, PN volume or number of PN-related morbidities. The limited data set from SPRINT Phase II Stratum I did not allow for any statistical relationship to be demonstrated. Some patients may have relatively small PN that occur in or around critical nerves/organs, thereby causing significant morbidities (for example, a small PN in the neck may impact the ability to breath, swallow, limit blood flow, cause pain) and reduced HRQoL. In contrast, other patients may have significantly larger PNs (for example on the trunk) that, although uncomfortable and visible, may have limited associated morbidities and therefore impact on HRQoL is lower.

g) Treatment effect modifiers

We concur that the criteria flagged are likely to be treatment effect modifiers. However, the small patient numbers and consequently small trial cohort within SPRINT Phase II Stratum I mean that there are insufficient data available to demonstrate any association. As such, to avoid developing an overly complex model with no robust data but rather reliance on a significant number of assumptions, which would be highly uncertain, the simple AUC approach has been utilised to demonstrate the potential benefit of selumetinib. As noted previously, this approach is likely to be very conservative as there is no negative impact on HRQoL considered for patients receiving BSC in the 'progressive' health state, despite the Natural History study showing that PN volume is likely to increase in the majority of patients, leading to further morbidities and associated reductions in HRQoL.

Clinical parameters

B3. Priority question. Please answer the following questions regarding PFS:

a) **Please clarify whether the definition of PFS focuses on the volume of only one PN. This seems to be the case looking at pages 79 and 80 of the CS, where partial response and progressive disease were defined in terms of *the target PN* compared with baseline. Also, in Table C31 the health state focuses on one main, large lump with an irregular shape. If that's the case, please explain what assumptions were made about patients with multiple PNs.**

b) **Please explain whether there is a link in the model between age, PN volume, PN-related morbidities and PFS.**

c) **On page 175 of the CS, it is mentioned that "*a simple annual progression rate was derived from the cumulative probability of progression as the data were too immature for parametric analysis*". Please explain why the PFS data were deemed immature for parametric analysis but the TTD data were not. Please clarify also whether this simple approach is equivalent to assuming an exponential distribution for PFS.**

d) **Please provide PFS estimates for the different age categories shown in Figure B3 separately.**

e) **Please explain what happens to PFS in the model when patients become 18 years old.**

f) **Please explain why is TTD substantially different from PFS and what happens to patients in the model after treatment discontinuation.**

a) Definition of PFS

In the SPRINT study, REiNS criteria for tumour response were to be used for the assessment of disease progression, which involved the analysis of one target PN and up to two non-target PN. A target PN is one that has been evaluated and deemed to be the most clinically relevant PN by the treating physician.[2] Since no clinically relevant non-target PN were reported during SPRINT Phase II Stratum I, assessment of progressive disease was based on target PN only. With selumetinib being a systematic treatment, it can feasibly be assumed that the treatment effect would also equally extend past the target PN to other PNs.

As noted in the previous response, the model simply considers the improvement in HRQoL associated with treatment with selumetinib. This is independent of the PN location, baseline PN volume and number of other PNs. Assuming that, as a systemic treatment, selumetinib may also reduce the volume of other non-target PNs, the current modelling approach is likely to be conservative as it foregoes any potential improvement that may be associated with such reductions.

b) Link between age, PN volume, PN-related morbidities and PFS

The current model does not consider any association between age, disease progression, PN volume or number of PN-related morbidities. The limited data set from SPRINT Phase II Stratum I did not allow for any statistical relationship to be demonstrated. Additional data with a longer duration of follow up would be needed in order to be able to explore these relationships further in the future. While we couldn't define strong relationship between these factors, the overall SPRINT Phase II Stratum I population still benefited from selumetinib treatment in terms of both PN volume reduction and PN-related morbidities. This holistic benefit evidenced in the clinical data should be considered when we appraising the modelling. Please refer to the answer to Question B2 for more further discussion of this point.

c) Parametric analyses

Most patients (84%) had not progressed by Year 3 of the SPRINT study, the data were therefore deemed too immature to conduct parametric extrapolations of PFS for the purpose of the cost-effectiveness analysis.[5]

The current approach would be equivalent to assuming an exponential parametric model. This was chosen over other parametric models as it minimises the number of

assumptions that were required (i.e. we only need to apply the annual rate recursively). With more complex parametric models, additional assumptions are made about the shape of the hazard function (i.e. Weibull or Generalised Gamma models which have two and three parameters, respectively). It was felt that use of a more complex model with relatively immature data would risk over-fitting to the observed data, especially given the limited number of patients available in the analysis.

As 42% of patients discontinued treatment from the 29th March 2019 DCO, it was possible to run parametric analysis of TTD.[5]

d) PFS estimates for different age categories

Figure 8 and Table 13 show the PFS data from the Natural History dataset. These data suggest that some patients, especially in the older age groups, may not have progressed. However, due to the wide age bandings and small patient numbers, those who have not progressed may represent those who have reached adulthood within the banding and reflect the PN stability that is assumed in the current model (i.e. the model assumes PN volume stabilises once a patient reaches 18 years of age). In addition, even if older age groups have slower tumour growth and progression rate, they have accumulated disease burden from already grown PNs. Therefore, better PFS at older age groups doesn't necessarily mean less morbidities or better HRQoL compared with younger age groups.

Figure 8. PFS in the Natural History study by age group (full analysis set)

Source: AstraZeneca Data on File.[37]

Table 13: PFS in the Natural History study by age group (full analysis set)

	<1 (n=2)	=>1 - <7 (n=39)	=>7 - <12 (n=32)	=>12 - <16 (n=16)	>16 (n=22)
Total number of events (progression or death) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of progressions n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median progression-free survival (years) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 1 year (%) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 2 years (%) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 3 years (%) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 4 years (%) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 5 years (%) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Progression includes deaths in the absence of progression. [b] Calculated using the Kaplan-Meier technique.
Source: AstraZeneca Data on File.[37]

e) PFS in patients ≥18 years of age

The model assumes that PN volume stabilises once a patient reaches 18 years of age, in both the selumetinib and BSC arm. No additional progression events will occur after a patient reaches 18 years of age in the model. If a patient who has received selumetinib progresses, their HRQoL is assumed to reduce linearly over a 5-year period back to the baseline value (i.e. that of a 'progressive' patient who has received BSC). If a patient reaches 18 years of age during this 5-year period, their HRQoL is assumed to persist at the level reached for the remaining duration of the analysis. It should be noted that due to the preventative nature of initiating treatment

with selumetinib and limiting PN growth in children, lifelong benefits are anticipated, as validated by several UK clinical experts who confirmed the importance of selumetinib in controlling tumour size into adulthood, whereby growth rates tend to plateau.[1]

f) Difference between TTD and PFS

As noted in the submission, TTD and PFS are modelled separately. Treatment with selumetinib reduces, stabilises or slows PN growth, thereby affecting PN volume; initiation of treatment in childhood targets the period where PN growth is most rapid. This is anticipated to have a preventative effect that limits the future lifetime impact of the target PN, including the number and severity of morbidities. The TTD data includes other reasons for discontinuation of treatment other than disease progression, including adverse events, investigator discretion, completion of treatment period, patient not willing to continue future treatment and severe non-compliance to protocol. With very few progression events over the follow-up period of SPRINT Phase II Stratum I, the PFS data shows only 16% of patients progressing by Year 3 when compared to the TTD data, which shows 42% of patients having discontinued selumetinib. This implies that there is residual benefit after discontinuing treatment with selumetinib; this assumption was validated by several UK clinical experts.

B4. Priority question. Please answer the following questions about treatment discontinuation:

a) **Please explain the reasons for treatment discontinuation as shown in Figure C2 (all reasons are not completely intuitive). Please clarify whether all these reasons are captured in the TTD analysis.**

b) **Please clarify why in Table C12 the total number of patients who discontinue seem to be [redacted] and not [redacted]. Note that the last 4 categories in Table C12 are not included in Figure C2. Please explain this as well.**

c) **On page 172 of the CS, it is mentioned that "*given the paediatric license for selumetinib (i.e., until the age of 18), eight years is an approximate maximum duration of treatment that is highly likely to be realised in clinical practice and is more than sufficient, based on the duration of treatment recorded in the SPRINT study*". Please explain how this is included in the model (is TTD truncated at 8 years?) since the TTD extrapolation seems to go beyond this time period.**

d) **TTD extrapolation is shown on page 179 of the CS. It is clear that assessing goodness of fit is difficult because all curves seem to provide a similar fit (and seem to overestimate observed data at the end of the observation period). Curve selection relied on expert opinion but it is unclear how clinical plausibility was defined. Furthermore, the sentence that "*Weibull resulted in the highest rate of discontinuation over the 100 year time horizon*" is confusing since it is mentioned that treatment is up to 8 years. Please explain how clinical plausibility was defined/judged. In particular, please explain (quantitatively) why the Weibull distribution was selected for TTD.**

a) Reasons for treatment discontinuation

Please refer to Table 14 below, for a description of the reasons for treatment discontinuation experienced by patients in the SPRINT Phase II Stratum I, up to the 29th March 2019 DCO (as outlined in Figure C2 of the core submission document).

Table 14. Reasons for treatment discontinuation during the SPRINT Phase II Stratum I

Reason for discontinuation	Description
Medical reasons for discontinuation	
Adverse event	If a patient experienced a toxicity requiring dose modification, selumetinib was withheld. Patients who were not receiving a clear clinical benefit from selumetinib permanently discontinued from selumetinib treatment if a toxicity did not resolve to Grade 1 or lower within 21 days of stopping treatment. Patients who were receiving a clear clinical benefit from selumetinib prior to experiencing the toxicity could continue treatment (at a reduced dose) if recovery from toxicity occurred within three months of stopping selumetinib. In determining whether additional treatment with selumetinib could continue after resolution of a treatment limiting toxicity, benefit was defined as either a partial response (≥20% decrease in PN volume), or stable disease (<20% increase or < 20% decrease in PN volume) in a patient who enrolled on the trial with progressive disease, or improvement of symptoms or function. For example, patients who experienced a toxicity requiring dose modification, whose toxicity recovered to meet study parameters within >21 days but ≤3 months, would have upon recovery, continued protocol therapy at a reduced dose, provided they had previously experienced clinical benefit while receiving selumetinib.

	If dose-modifying toxicity recurred in a patient who had resumed treatment after two dose reductions, the patient would be removed from treatment.
Disease progression	Patients who completed a treatment cycle could receive another cycle at the same dose level unless they experienced disease progression, defined as an increase in the volume of the target PN by 20% or more, compared to baseline or the time of best response after documenting a partial response. The appearance of new PN or unequivocal progression of existing non-target PN was also considered progressive disease.
Investigator discretion	Treatment could be discontinued at the discretion of the principal investigator (i.e. in advance of the end of the treatment period [please see 'Treatment period completed' below]), if this was felt to be in the interest of the patient for medical reasons.
Treatment period completed	For patients who had documented disease progression within approximately 1.5 years prior to trial entry there was no limit to the duration of treatment, as long as the patient met the requirements for further treatment. For patients with no previous documented history of disease progression within the 1.5 years prior to trial entry, the duration of the study was limited to 2 years, if no imaging response (PN volume decreased by ≥20%) was observed. Patients in Phase II of the SPRINT trial who were removed from treatment after 2 years for reasons other than toxicity or progression with stable disease continued to be monitored with MRI and volumetric analysis every 4–6 months. If the PN demonstrated progression (volume increase ≥ 15%) within approximately 2 years of stopping selumetinib, treatment with selumetinib may have been restarted with the goal to stop further PN growth. In these patients, treatment could continue as long as the PN remained stable or responsive (<20% increase in the PN volume). For patients with no previous documented history of disease progression within the 1.5 years prior to trial entry, who did show imaging response, the treatment duration was not be limited unless the patient experienced subsequent disease progression or met other discontinuation criteria. However, treatment may have been discontinued earlier at discretion of the institutional principal investigator if this was felt to be in the best interest of the patient (please see 'Investigator discretion' above).
Non-medical or administrative reasons for discontinuation	
Patient not willing to continue future treatment	A patient was removed from treatment if the patient refused to receive further treatments. The reasons for refusal of further treatment were noted on the patient's case report form.
Severe non-compliance to protocol	A patient was removed from treatment due to serious protocol violation, as determined by the principal investigator.

Abbreviations: PN: plexiform neurofibroma; MRI: magnetic resonance imaging.

Source: AstraZeneca Data on File (SPRINT Protocol).[2]

In addition to the reasons for discontinuation outlined above, additional reasons for discontinuation were detailed in the trial protocol (but were not experienced by any study participants):

- A patient who underwent complete surgical resection of their PN (thus rendering them with no evidence of disease) was required to discontinue treatment
- A patient who developed a concurrent serious medical condition that might preclude or contraindicate the further administration of selumetinib was removed from study treatment. A patient who became pregnant would immediately have been taken off therapy

The model considers treatment discontinuation due to any reason, as listed in Figure C2 of the submission document. Full details of the reasons for removal of patients from treatment can be found within Section 3.8 of the SPRINT protocol.[2]

b) Number of discontinuing patients

As described in Section 9.4.6 of the core submission document, in the period up to the 29th March 2019 DCO, [redacted] patients had **discontinued** selumetinib.[14]

In addition to reasons for discontinuation, Table C12 in the core submission document also detailed the number of patients who had **terminated** their involvement in the study ([redacted]). Patients who were off protocol therapy (due to treatment discontinuation) were to be followed until they met the criteria for 'off study'.[14] Full details on the off study criteria can be found within the SPRINT protocol.[2]

The reasons for termination included 'voluntary discontinuation' ([redacted]), 'loss to follow-up' ([redacted]) and 'other' ([redacted]). Of the remaining [redacted] patients who had discontinued treatment but who had not terminated the study, [redacted] patients were re-treated, as per the clinical study protocol (please see page 9 of the 90 day safety update[14] for the individual patient data). [redacted] patients continued to be involved in the study but were not on the study treatment (i.e. were 'off therapy' but not 'off study').[14]

Please see Table 15 below, which has been included to clarify the difference between the number of patients discontinuing treatment, and those terminating the study.

Table 15. Proportion of patients who discontinued and terminated study treatment in SPRINT Phase II Stratum I

Reason for discontinuation	Selumetinib (N=50), n (%)
Patients enrolled[a]	[redacted]

Patients who received at least one dose of selumetinib	[redacted]
Patients ongoing selumetinib at data cut-off[b]	[redacted]
Discontinued study treatment[c]	[redacted]
Adverse event	[redacted]
Disease progression	[redacted]
Investigator discretion	[redacted]
Treatment period completed	[redacted]
Patient not willing to continue future treatment	[redacted]
Severe non-compliance to protocol	[redacted]
Patients who were re-treated	[redacted]
Patients ongoing study	[redacted]
Patients who terminated study	[redacted]
Voluntary discontinuation	[redacted]
Lost to follow-up	[redacted]
Other	[redacted]

[a] Informed consent received. [b] Does not include re-treated patients. [c] Includes re-treated patients; two patients discontinued treatment due to reasons of "Treatment period completed" and "Disease progression on study" respectively and were subsequently re-treated (please see below).
Source: AstraZeneca Data on File (90 day safety update).[14]

c) Duration of selumetinib treatment

The average age of the cohort on model entry is assumed to be 10 years, which is aligned to the baseline characteristics of SPRINT Phase II Stratum I.[7] Since it is assumed that patients will experience no HRQoL change after adulthood, patients will stop treatment after 8 years and the corresponding costs are no longer applied. It is noted that the TTD curve presented in the model does not illustrate that the treatment with selumetinib stops and actually shows the full extrapolation. However, in the model selumetinib treatment costs are no longer applied after 8 years. This assumption can be varied in the model and removing the 8-year truncation increases the ICER to [redacted] (from £93,169 in the base case).

d) Selection of TTD extrapolation

All parametric models were presented to a group of clinicians with prior experience of similar survival analysis extrapolations. It was explained that the model assumed that PN volume was likely to be stable in adulthood. With minimal experience of long-term treatment with selumetinib, the clinicians felt that treatment continuation into adulthood was likely to be low (as there would be minimal benefit from continuing treatment into adulthood) and therefore the Weibull assumption seemed a credible assumption for the base case. All distributions were explored in scenario analysis and the impact is reasonable with ICERs varying from £[redacted] to [redacted] per QALY. As noted above, in the base case treatment is limited to 8 years;

however, if this assumption is replaced with the TTD curves alone, the impact is larger. The results of excluding the 8-year limit for all of the alternative parametric distributions are presented in Table 16 with the ICER ranging from [redacted] to [redacted] per QALY.

Table 16. Scenario analysis – time to discontinuation parametric distributions excluding treatment limit

TTD parametric distribution	Incremental costs (£)	Incremental QALYs	ICER
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TTD: time to discontinuation.

B5. Priority question. The magnitude and duration of the residual benefit after discontinuation is unclear. On page 176 of the CS, it is mentioned that *"the SPRINT study demonstrated that selumetinib results in durable improvements in HRQoL; in the model, this benefit persists until the patient progresses, even if the patient has discontinued treatment"*. While this seems to be plausible, we would like the clarification whether this residual benefit might depend on treatment duration or the cause for discontinuation.

For example, it might seem reasonable to assume that there is a residual benefit for patients treated with selumetinib but provided that patients were on treatment for long enough time (e.g. patients discontinuing treatment in a few months should not get any or little residual benefit). It also seems reasonable to assume that it is not the same discontinuing because treatment did not work (patient would be progressive and should not receive any or little residual benefit) than discontinuing because the patient became 18 years after 8 years of successful treatment.

Please include in the model the option to select the minimum time on treatment needed to experience a residual benefit (e.g. 1, 2, 3… etc. years) and justify its most plausible value.

There was a highly variable PN growth rate and limited sample size in SPRINT Phase II Stratum I (only six patients had progressed in the SPRINT study by Year 3),[5] meaning there are limited data to link duration of treatment to durability of response. The model therefore considers the best available data, with regards to treatment continuation and progression, and includes these separately, thereby removing any assumptions between discontinuation and progression.

While the model doesn't consider the cause for discontinuation or the treatment duration directly, it does consider the age at which a patient discontinues, which will, in part, reflect treatment duration.

If a patient who has received selumetinib progresses, their HRQoL is assumed to reduce linearly over a 5-year period back to the baseline value (i.e. that of a 'progressive' patient who has received BSC). If a patient reaches 18 years of age during this 5-year period, their HRQoL is assumed to persist at the level reached when the patient reached 18 years of age, for the remaining duration of the analysis. The durability of response is therefore implicitly linked to reaching adulthood, this approach was validated by UK clinical experts who confirmed the importance of initiating treatment with selumetinib and limiting PN growth in children and controlling tumour size into adulthood, at which point growth rates tend to plateau.

Given the structure of the model, patients who discontinue due to the disease progression are considered differently to patients who discontinue due to other reasons. The former will encounter utility reduction as soon as they discontinue the treatment while the latter will experience residual benefit until the disease progresses.

Insufficient data are available to establish an explicit link between time on treatment and the associated residual benefit, requiring a pragmatic assumption to be applied. In the SPRINT Phase II Stratum I, the median time to response was 8 cycles and the median time to best response was 16 cycles (1.2 years).[5] Furthermore, HRQoL improvement was observed from pre-cycle 3 and plateaued from the pre-cycle 13 assessment. Therefore, it's reasonable to assume that the residual benefit on PN volume and HRQoL will be maintained if discontinuation happens after one year of treatment. Application of residual benefit after the treatment discontinuation in the model was also validated and supported by clinicians during model validation with UK clinical experts (see Section 10.6.2 of the company submission).[1]

Therefore, the current model approach provides a reasonable proxy for estimating durability of response and residual benefit. Furthermore, the application of longer minimum time on treatment being necessary to experience a residual benefit (2, 3…etc. years) in the model would be difficult given the insufficient data to support the assumption.

B6. On page 100 of the CS, it is mentioned that *"the median time to initial response in SPRINT Phase II Stratum I was 8 cycles (range 4–20), and the median time to best response was 16 cycles (range 4–36). Of the 35 patients who had confirmed PR to selumetinib, 28 (80%) had a durable response to selumetinib treatment, defined as a response lasting for more than one year"*.

Please clarify whether (and how) duration of treatment response was included in the model.

Patients who receive selumetinib are assumed to experience a response over the first year of treatment. These patients are assumed to remain in this progression-free response state for the duration of the analysis unless they progress, as modelled by progression status (PFS). If a patient who received selumetinib progresses, their HRQoL is assumed to reduce linearly over a 5-year period back to the baseline value (i.e. that of a 'progressive' patient who has received BSC). If a patient reaches 18 years of age during this 5-year period, their HRQoL is assumed to persist at the level reached at this point for the remaining duration of the analysis.

Adverse events

B7. Priority question. Please answer the following questions regarding adverse events (AEs):

a) **On page 19 of the CS, it is mentioned that "Selumetinib monotherapy has a generally predictable and manageable safety profile in paediatric patients with NF1 PN. AEs were usually mild or moderate in severity". However, [redacted] are reported to discontinue treatment due to AEs, which may be argue to be a substantial proportion. Please describe what AEs led to treatment discontinuation and clarify whether these are included in the model or not. If needed, please provide relevant details for these patients.**

b) **Please explain the criteria for including AEs in the model. For example, AEs included in the model (Table D7) do not match with those reported in Table C25 (most common Grade ≥3 AEs in SPRINT). Please explain why not all AEs in Table C25 were included in the model. Also, the proportion of patients with serious AEs related to selumetinib is [redacted] in Table C23. These are further summarised in Table C26. Please explain why not all these AEs (e.g. anaemia) were included in the model.**

c) **Please explain in detail how AE costs were calculated (e.g. how Table D7 was used, what unit costs, etc.).**

d) **Please clarify whether dose interruptions, reductions and discontinuations due to AEs are included in the model and how.**

e) **On page 153 of the CS, it is mentioned that "It can therefore be assumed that the adverse events will have a minimal impact on HRQoL". This is not completely clear based on the evidence presented (a substantial proportion of patients experienced grade >3 or serious AEs, also leading to treatment discontinuation). Please consider adding AE-related disutilities to the model.**

a) AEs leading to treatment discontinuation

Table 17 provides an overview of the AEs leading to treatment discontinuation experienced by patients in SPRINT Phase II Stratum I up to the 29th March 2019 DCO.

The AEs leading to discontinuation of selumetinib were distributed across a wide range of system organ classes, with no single type of AE leading to discontinuation in more than one case. [redacted] of the AEs leading to treatment discontinuation were amongst those most commonly experienced in the patient population ([redacted]).[14] However, only [redacted] of patients that experienced [redacted], and only [redacted] of patients who experienced [redacted], discontinued selumetinib treatment, indicating that these AEs were generally manageable.[14]
[redacted][9]

The majority of PN are symptomatic, and are associated with a wide range of morbidities affecting multiple organ systems (dependent on the location and size of the PN).[10-13] In light of the severity of baseline morbidity, and the paediatric population, a [redacted] discontinuation rate due to AEs is not considered substantial.[14]

Table 17. SPRINT Phase II Stratum I: Adverse events leading to discontinuation of selumetinib, by system organ class and preferred term

System organ class/Preferred term	Selumetinib (N=50), n (%)[a]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[a]Number (%) of patients with an AE leading to discontinuation of selumetinib, sorted by international order for SOC and alphabetically for PT. Patients with multiple AEs leading to discontinuation of selumetinib are counted once for each SOC/PT.
Source: AstraZeneca Data on File (90 day safety update).[14]

The individual patient reports for the patients who experienced AEs leading to discontinuation highlight that, through appropriate management, the AEs stabilised and completely resolved.

Table 18. Description of AEs leading to treatment discontinuation

Patient identification	Description of AE leading to treatment discontinuation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MPNST: malignant peripheral nerve sheath tumour; PN: plexiform neurofibroma; SAE: serious adverse event.
Source: AstraZeneca Data on File (Individual Patient Reports).[9]

Of the AEs leading to discontinuation of selumetinib, the cases of diarrhoea and paronychia ([redacted]% of all AEs leading to treatment discontinuation)[14] were costed in the model as these occurred in greater than 5% of patients. In addition, the TTD data include discontinuation due to AEs. The TTD also included discontinuation due to a number of other factors and therefore for simplicity no costs were incorporated for these discontinuations. We acknowledge that this is a limitation of the approach but assume that the relative treatment costs and impact on HRQoL would be low relative to the underlying disease.

b) Criteria for inclusion of AEs in the model

Common to many models, and for simplification, only Grade ≥3 AEs in SPRINT that occurred in greater than 5% of patients (Table 19) were included, on the basis that these AEs are of the greatest clinical relevance.

Table 19. Adverse events reported in SPRINT and included in the economic analysis

Adverse event	Percentage of patients (n/N)	Mean duration, days (SD)
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Pyrexia (Fever)	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]

Source: AstraZeneca Data on File (90 day safety update).[14]

c) Calculation of AE costs

As noted in Section 12.3.7 of the submission document, treatments for the respective AEs were identified and associated product prices informed by the BNF (Table 20).[39]

The costs of AEs can be considered small relative to the cost of selumetinib and so their inclusion/exclusion have minimal impact on the final ICER (as demonstrated in Table D24 of the submission document).

Table 20. Cost of adverse events with selumetinib

Adverse event	Treatment	Estimated cost per event	Proportion of patients experience AE
Diarrhoea	Loperamide (Various doses – assumed a single pack would resolve symptoms. 2mg, 30 tablets at £1.58 per pack)	£1.84	[redacted]
Vomiting	Ondansetron (4mg, two times per day for up to 5 days– 10 tablets at £1.07 per pack)	£1.07	[redacted]
Pyrexia (Fever)	N/A	N/A	[redacted]
Hypoxia	N/A	N/A	[redacted]
Paronychia	Flucloxacillin (250mg four times a day for 7 days – 28 caps at £1.72 per pack)	£37.71	[redacted]
Dermatitis acneiform	Metronidazole cream (Typical duration of symptoms was 4 months, assume one 40mg unit would be sufficient for 1 month treatment. 40g of, 7.5mg metronidazole per gram, at £9.88 per unit)	£3.44	[redacted]
Weighted average cost of adverse events per patient		**£[redacted]**	

Abbreviations: N/A: not applicable.
Source: BNF;[39] AstraZeneca Data on File (90DSU).[14]

d) Dose interruptions, reductions and discontinuations due to AEs

The model does not consider dose interruptions nor dose reductions. This assumption is considered to be conservative, as including either would be expected to result in lower costs for selumetinib.

The TTD data applied in the model include patients who discontinue due to AEs.

Duration of exposure data from the SPRINT study suggest that actual treatment days totalled [redacted], compared to a total treatment duration of [redacted] days. It could therefore be inferred that over the duration of the study the delivered selumetinib

dose could be reduced by approximately 7.7% per annum to account for dose interruptions and reductions. If this is factored into the base case analysis, the total cost of selumetinib is reduced to [redacted] and the associated ICER is reduced to [redacted] (Table 21).

Table 21. Scenario analysis incorporating dose interruptions and/or dose reductions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

e) Impact of AEs on HRQoL

As noted in Table D7 of the submission (replicated in Table 19), the mean duration for the majority of AEs considered was short. Given the uncertainty in the underlying HRQoL data, it was assumed that the relative impact of incorporating HRQoL for these AEs would have minimal impact on the ICER and so specific AE figures were excluded for simplicity. However, it should be noted that due to the frequency of skin rash (dermatitis acneiform) the decision was made to only include this in the treated health state vignette to reflect the AE profile; the model therefore does already partially reflect the AE profile of selumetinib.

Health-related quality of life (HRQoL)

B8. Priority question. Please answer the following questions regarding caregiver disutility.

a) **The base case analysis assumes that parents/carers experience the same relative HRQoL decrement as patients. This assumption seems unjustified and results in a caregiver disutility which is substantially higher than other values used in previous technology appraisals (TAs) or highly specialised technologies (HSTs, e.g. HST8 or HST11). While we acknowledge the current uncertainty and lack of guidance regarding the implementation of caregiver disutility in economic evaluations, we would like further justification for this assumption and, if deemed valid, explain why this is substantially higher than the ones used in previous submissions.**

b) **The base-case analysis assumes that starting from a mean age of parents of 30.6 years at childbirth, a general population utility value is determined using the regression algorithm from Ara and Brazier 2010 and adjusted accordingly each model cycle. While again we acknowledge the current uncertainty regarding the implementation of caregiver disutility in economic evaluations, the ERG feels this method might be unnecessarily complex, relying on two assumptions which are uncertain: the mean age of parents and that parents' utilities are based on general population utilities. Please include in the model a simpler method (like the one used in HST8) where the caregiver disutility is directly applied in every model cycle (up to the patient's age that is considered appropriate). Please do not remove the current method from the model because, given the aforementioned uncertainty in methodology, it is interesting to compare potential differences in results obtained with each of the methods.**

c) **Page 49 of the CS refers to a cross-sectional study of US NF1 PN carers (n=95), in which around 50% of carers reported a burden ranging from mild to severe. Furthermore, amongst 95 US NF1 PN carers, an average of 17.2% of regular daily activities were hindered by providing care for their child with NF1 PN. Therefore, from this study it can be concluded that carer burden is not experienced by all parents. However, the model seems to include the full burden effect for all parents (1.4 in total but not a proportion as suggested by the US study). Please justify the modelling assumption and discuss the role of the US cross-sectional study.**

d) **Please allow the model to vary caregiver (dis)utility independently of the patients' utility.**

a) HRQoL decrements for parents/carers

We acknowledge that the approach taken is novel and therefore associated with uncertainty. Given the lack of disease-related HRQoL data in both patients and parents/carers, a range of alternative approaches were considered. It was felt that a static point estimate reduction does not reflect the variability in HRQoL considered in

the patient cohort; for example, if the relative impact in HRQoL for a treated or untreated patient reduced intuitively, the relative impact on the parent/carer should also reduce. The model therefore utilised the relative HRQoL reduction approach in the base case; however, an absolute reduction was also considered and presented in the submission (Table D31).

This hypothetical approach was discussed with clinicians; all of the clinicians interviewed felt that inoperable, symptomatic PNs would also have a negative impact on the HRQoL of parents and carers. The negative impact is driven by several factors, including the lack of treatment options, the inability to alleviate suffering of child, and the uncertainty over PN progression (i.e. periods of continuous or rapid tumour growth). They felt that the reduction in HRQoL was likely to occur irrespective of PN heterogeneity. For example, if a patient has a PN that compresses their airway, parents/carers experience constant fear that the child may stop breathing. For patients with facial PNs, there may be less concern around functional impairment but instead the social aspect of facial disfigurement (e.g. acceptance, attitudes) may reduce parent/career QoL. When treatment stabilises/shrinks a PN and/or improves symptoms, parents/carers experience psychological improvements that are likely to be reflected in QoL measures and in the absence of any robust data, it was felt that proportional reduction was a reasonable approach in the base case.

b) Age of parents/carers

The model includes the Ara and Brazier 2010 algorithm in patients to avoid overestimating any long-term HRQoL benefit and was incorporated to reflect a point raised in NICE DSU TSD 12.[40] In this, the authors comment that in models with long time horizons it is reasonable to assume that average baseline utility values for the general population will not remain constant across the time horizon and are likely to decrease over time as comorbidities accrue with age. It seems to be a reasonable assumption that the health status of parents or carers of NF1 patients would not differ from the general population, controlling for age and sex. The authors also state that “data from the general population show that the mean HSUV for subgroups of the general population is never equal to full health irrespective of age or gender”.[40] Removal of the age adjustment in the patients from the model results in an improved ICER of [redacted] per QALY.

With the inclusion of this algorithm in the patient cohort, it was also adopted for the parent/carer QoL estimates.

It should be noted that the model already facilitates the ability to include an absolute reduction; this is applied to the age-adjusted figure but because it is applied as an absolute reduction the relative effect should be the same. In the HST 8 and 11 submissions, the manufacturers identified a systematic review of disutilities of illness for caregivers and families, which reported a disutility of 0.08 for parents of children with activity limitations.[41] A scenario analysis considering an absolute reduction of -

0.08 per carer (as utilised in HST 8 and 11) was considered and the results are presented in Table D31 of the submission (also presented below as Table 22).

Table 22. Parent/carer utility – absolute utility decrement of 0.08 in BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

c) Cross-sectional study of US NF1 PN carers

While as part of this study an average of 17.2% of regular daily activities were hindered by providing care for a child with NF1 PN, this is only one aspect of QoL. Within this study, commonly reported health conditions among caregivers included anxiety (48.4%), depression (34.7%) and obesity (25.35%), indicating that the mental health burden on caregivers is likely to be high.[42]

The study also does not specifically look at the impact on caregivers for the cohort of interest, i.e. patients with symptomatic, inoperable PNs. During AZ qualitative interviews, clinicians advised that the inoperability of symptomatic PNs can place a considerable mental burden on parents/carers. The US study findings are therefore likely to be an underestimation of the true parent/carer burden for patients with NF1 and symptomatic, inoperable PN.

d) Variation of parent/carer disutility

As noted above, the model already allows for the consideration of a utility decrement for a caregiver that is independent of the patients' utility. A scenario analysis considering an absolute reduction of 0.08 per carer (as utilised in HST 8 and 11) was considered and the results are presented in Table D31 of the submission (and Table 22 above).

B9. Priority question. Please provide the complete vignette study (methods and results by individual so that any differences between patients and clinicians can be assessed). Please clarify whether the health states of the vignette study are in line with the model health states. Please explain also how it can be concluded that the findings from the vignette study are in line with those from SPRINT data (PedsQL).

Detailed vignette study method and results are described in Appendix A.

Time trade-off (TTO) valuation was conducted with 100 members of the general population and the mean utility scores from this exercise are presented in the result. Vignettes include two core health states used in the model; a stable (non-progressive) state for the patients who received selumetinib and a progressive state for the baseline and for the patients who have not received selumetinib. PN location-specific vignettes were also developed and evaluated, but the base case model used the utility scores from vignettes with unspecified tumour location. As described in table C35 of submission, differences in utility score with and without selumetinib were similar between PN location-specific vignettes and non-specific vignettes.

Based on the vignette study, the utility value at baseline (progressive disease) was [redacted], which increased to [redacted] in the stable (non-progressive) state. In SPRINT Phase II Stratum I, PedsQL total score change from baseline to pre-cycle 13 was [redacted] (self-report) and [redacted] (parent-report), and from baseline to pre-cycle 25 was [redacted] (self-report) and [redacted] (parent-report). Results from the vignette study reflect this improvement of HRQoL observed from SPRINT Phase II Stratum I.

B10. Priority question. Please answer the following question regarding utilities:

a) **Please show how the utility estimates in Table C34 were derived.**

b) **Please discuss whether these utilities are in line with a priori expectations (e.g. if there are "similar" diseases, how do these utilities compare to the utilities in those diseases?).**

c) **In the CS, it is argued that a substantial proportion of the benefits of selumetinib are associated with improvements in HRQoL for both patients and their parents/carers. Please explain what the expected role of age in HRQoL is. In particular, please clarify whether a difference in utility between adult patients and children/adolescent patients should be expected. If that's the case, please include age-dependent utilities (other than those resulting from applying Ara and Brazier decrement) in the model.**

d) **Please clarify also whether a difference in caregiver (dis)utility should be expected depending on whether the patient is an adult or a child/adolescent. If that's the case, please include caregiver (dis)utilities dependent on patient age in the model**

e) **Finally, the CS seems to suggest that there might a link between PN volume and PN-related morbidities and HRQoL. However, the model assumes that the HRQoL of patients with progressive PN growth remains constant for the duration of the analysis. Please discuss the plausibility of this assumption and, if deemed plausible, please include in the model utilities depending on PN volume and number of PN-related morbidities.**

a) Derivation of utility estimates

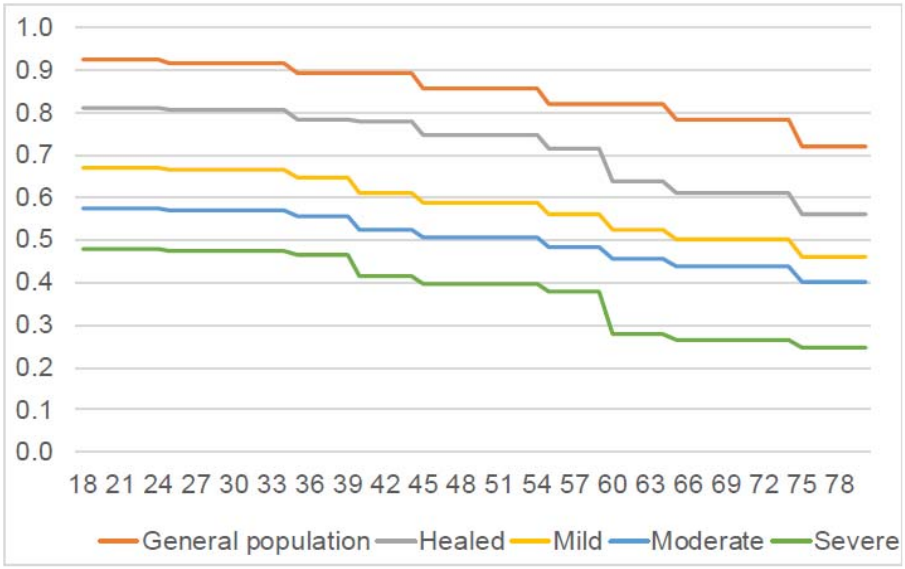
Time Trade Off (TTO) interviews with 100 members of the general public, using different health state vignettes, were used to estimate the health state utility values outlined in Table C34. Please refer to Appendix A for more detail on methods and results from the TTO interview.

b) Discussion of utility estimates

It is difficult to find similar disease to NF1 PN. However, insight might be gained from the NICE appraisal of burosumab (HST8). Burosumab is indicated for the treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. XLH is a rare, chronically debilitating and deforming disease caused by mutations in the PHEX gene. Clinical expression of XLH is widely variable, partly due to genetic differences. Symptoms of XLH usually begin in early childhood with skeletal abnormalities and it may progress to include further skeletal and non-skeletal manifestations over time. Patients often need orthopaedic surgery to correct bone deformities. NF1 PN share similar disease characteristic, such as being a rare genetic disorder diagnosed early in the lifetime, and having a lifelong impact with debilitating and deforming symptoms. It also displays substantial heterogeneity due to different phenotypes of the underlying mutation.

In HST8, utility scores of healed, mild, moderate and severe XLH were presented (as per Figure 9). As selumetinib is targeting symptomatic and inoperable NF1 PN, we may compare this with severe XLH patients who have utility score of about 0.48 at the age of 18 years. This is improved to about 0.67 if symptoms become mild and about 0.81 if the disease is healed. This numbers are relatively similar to the utility score results from the vignette study in NF1 PN.

Figure 9. Utilities by age (for XLH patients)



Source: NICE HST 8 (burosumab for treating X-linked hypophosphataemia in children and young people), Final Evaluation Determination committee papers.

c) Role of age in HRQoL

The impact of age on HRQoL is uncertain. In the earlier years of the disease, during which the PN volume increases and patients become symptomatic, HRQoL is expected to decrease. However, due to the variability in PN location, PN size, rate of PN volume change over time and associated impact on HRQoL, it is not possible to correlate this impact directly with age. Similarly, when patients reach adulthood, PN volume is assumed to become more stable; however, it is unclear if patients will become accustomed to the comorbidities and view the HRQoL more favourably or if the continued burden of the accumulated comorbidities may result in further decrements in HRQoL over time.

There is little HRQoL data associated with NF1 patients and very limited data specifically available for NF1 patients with symptomatic, inoperable PN, especially when considering age specifically. It is therefore inappropriate to incorporate this into the analysis.

The current approach, which simply considers a treated/untreated HRQoL value, is likely to be conservative as it assumes that patients who enter the model receiving BSC will maintain this level of HRQoL for the model duration. This is despite evidence from the Natural History study that shows PN volume is likely to increase substantially from the point of entry into the model.

d) Parent/carer (dis)utilities dependent on patient age

The impact on a parent/carer is likely to vary depending on the severity of the comorbidities experienced by the patient. In some instances, as a patient moves into

adulthood the need for support may reduce, while for others it may persist. In the model base case, the impact on the parent/carer is assumed to last until the patient reaches 18 years of age. This was considered in scenario analyses (Tables D28-30 of the submission), which consider the impact on the parent/carer persisting until the patient reaches 24 years of age, persisting until the parent/carer reaches 64 years of age, or persisting for the parent/carer's expected lifetime. As could likely be anticipated, the longer the impact persists, the greater the QALY improvement and the lower the associated ICER.

It could be expected that the more significant the morbidities a patient experiences, the greater the burden on the parent/carer will be, and the longer the associated impact is likely to persist. Therefore, selumetinib would be more cost-effective.

e) Link between PN volume and PN-related morbidities and HRQoL

Progression of PN (defined as a volume increase of ≥20% compared to baseline PN volume, or an increase of ≥20% from best response if a patient had had a PR) shows a clear association with an increase in the number and severity of PN-associated morbidities (see Section 6.1 of the company submission). However, the location of the PN is also a significant confounding factor; patients with a relatively small PN in one location may have significant morbidities, compared with others with a significantly larger PN in another location who may have far fewer and/or less impactful morbidities. While no direct quantitative link between PN volume and PN-related morbidities/HRQoL could be definitively established given the limited data set, it is reasonable to assume that increased PN volume will likely negatively impact HRQoL, irrespective of location. The current assumption that HRQoL in 'progressed' patients remains stable for the model duration is therefore highly likely to be conservative as most patients receiving BSC will experience PN volume growth (especially younger patients who experience greater PN volume changes) and potential decrease in HRQoL.

B11. Priority question. Please perform a mapping of the PedsQL trial data to the EQ-5D to provide some validation of the utility values obtained by the vignette study. Several mapping functions are available. Despite the available mapping functions being estimated in different patient populations it is important to have some estimate of the utility based on the trial data for at least validation purposes. Baseline data could provide an estimate for off treatment utility and post-baseline measurements an estimate for on treatment.

The only EQ-5D utility mapping function for the PedsQL we are aware of is from a study by Khan *et al*; however, this study has been criticised on a number of points.[43]

The data that the mapping study was based on was derived from 11–15 year old children and so it is possible that this may limit the applicability of the mapping

function when used for younger children. The PedsQL includes age-specific forms, and six different versions covering different age groups and responders were used in the SPRINT trial: Children (8–12 years of age), Teenagers (13–18 years of age), Parents reporting for children (8–12 years of age), Parents reporting for teenagers (13–18 years of age), Parent reporting for toddlers (2–4 years of age), Parents reporting for young children (5–7 years of age).

In addition, the Khan *et al*. study has been criticised because the sample of children who completed the questionnaires were all secondary school children, and were not recruited based on having health problems. This meant that the scoring range of the data was very limited, which has a limiting effect on the ability to map between the two measures.

In consequence, we believe that the mapping analysis does not appropriately reflect the utility score of NF1 PN patients in the wider age range (3–18 years of age) from the SPRINT trial. Furthermore, the utility scores from the vignette study can be considered a better option for the modelling, as they reflect the preference of the general public regarding the NF1 PN specific health status. Any improvements of HRQoL over the study period can also be confirmed through PedsQL scores themselves without the need of applying mapping algorithms.

B12. Please consider how appropriate it is to use age decrements from Ara and Brazier in a paediatric population given that these were estimated using the adult EQ-5D-3L based on data from individuals aged 16+.

A large proportion of the utility benefit of selumetinib is realised from the extended time horizon which continues into adulthood. It was therefore deemed appropriate to include the Ara and Brazier 2010 algorithm to avoid overestimating any long-term HRQoL benefits and to reflect recommendations from NICE DSU TSD 12 (as described in the response to Question B8b).[40] We are unaware of similar algorithms for paediatric cohorts. The inclusion of the algorithm may be conservative for selumetinib and can be deactivated in the model. In scenario analysis, removing the Ara and Brazier 2010 algorithm results in an ICER of [redacted] per QALY (compared to the baseline ICER of £93,169 per QALY; Table 23).

Table 23. Excluding the Ara and Brazier 2010 utility adjustment

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

B13. Table C35 shows the utility value differences with and without selumetinib. Please provide the absolute estimated utility values (not only the differences). Please explain also the impact of multiple PN-related morbidities in HRQoL and whether this is included in the model.

Table C35 from the submission document was updated as below to incorporate the absolute utility values (Table 24).

Table 24. Utility value differences with and without selumetinib

PN location	Utility value with Selumetinib	Utility value without Selumetinib	Difference in utility value with and without selumetinib
Unspecified (base case)	[redacted]	[redacted]	[redacted]
Face	[redacted]	[redacted]	[redacted]
Trunk	[redacted]	[redacted]	[redacted]
Leg	[redacted]	[redacted]	[redacted]

Abbreviations: PN: plexiform neuroma.

Due to the significant heterogeneity of PN-associated morbidities, neither the specific impact of individual morbidities nor multiple morbidities have been considered within the model. However, the model utilises the TTO utilities in which the vignettes attempt to reflect the heterogeneity of PN-associated morbidities.

Resource use and costs

B14. Priority question. Please answer the following question regarding resource use and costs:

a) **Please explain in detail how the values in Tables D10 and D11 were derived.**

b) **Please explain in detail how <u>all</u> costs in the model were derived.**

c) **Please explain whether all relevant costs for health care resource use in relation to general disease management and monitoring (e.g. physician visits, visits to other health care providers, etc.) have been included, and, if not, please make sure to include all relevant costs.**

d) **Table B4 describes the established clinical management for PN-associated morbidities (pain, motor, airway, bladder and bowel, and**

vision). Please explain whether and how all these morbidities were included in the cost calculations.

e) **On page 16 of the CS, it is mentioned that "*There are currently no available or approved pharmacological treatments to cure, prevent or reduce the volume of inoperable PN; patients must rely on symptomatic management only, ranging from pain medication to interventions such as tracheostomy to alleviate severe airway morbidities*". Please clarify whether and how symptomatic management was implemented in the model (e.g. costs).**

a) Treatment dosing and cost calculations

As detailed in Section 12.3.5 of the submission, during SPRINT Phase II Stratum I, selumetinib was administered according to BSA-based dosing, with doses rounded to the nearest 5–10 mg using a dosing nomogram (Table 25). Selumetinib is administered at a dose of 25 mg/m^2 BSA, twice daily (approximately every 12 hours), up to a maximum single dose of 50 mg.[44] The cost per dose (Table 25) is calculated based on the number of capsules required to deliver the specified dose and the respective cost per capsule. This is then scaled up to a daily cost and then an annual cost, as shown in Table 26.

Table 25. Dosing nomogram from SPRINT

BSA (m^2)	0.55–0.69	0.70–0.89	0.90–1.09	1.10–1.29	1.30–1.49	1.50–1.69	1.70–1.89	1.90–2.04
Dose required (25 mg/m^2/dose)	20 (morning) 10 (evening)	20	25	30	35	40	45	50
Capsules required to deliver dose								
10 mg	1.5	2	-	3	1	4	2	-
25 mg	-	-	1	-	1	-	1	2
Cost per dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area.

Table 26. Costs-per-patient associated with selumetinib

BSA (m^2)	Dose (mg)	Cost/dose	Cost/day	Cost/annum
0.55–0.69	20 (morning) 10 (evening)	[redacted]	[redacted]	[redacted]
0.70–0.89	20	[redacted]	[redacted]	[redacted]
0.90–1.09	25	[redacted]	[redacted]	[redacted]
1.10–1.29	30	[redacted]	[redacted]	[redacted]
1.30–1.49	35	[redacted]	[redacted]	[redacted]
1.50–1.69	40	[redacted]	[redacted]	[redacted]
1.70–1.89	45	[redacted]	[redacted]	[redacted]
1.90–1.94	50	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area.

b) Detailed cost calculations

Due to the heterogeneity in patient management and symptomatic management, the model conservatively considers only a limited number of cost items. Treatment cost of selumetinib is based on the list price and presented results also include a simple patient access scheme (PAS) discount submitted to NICE PAS Liaison Unit (PASLU). With the exception of two additional MRIs, with an assumed cost of £264.50 per MRI examination (based on highest outpatient MRI cost from 2018–19 NHS reference costs [RD07Z]), it assumed that there are no additional costs associated with either NF1 management or the administration of selumetinib.

The only other costs considered in the analysis are pain medication costs (as detailed in Section 12.3.5 of the submission) and those of managing treatment-related AEs (as detailed in Section 12.3.7 of the submission).

All concomitant pain medications used during the study were identified from the SPRINT CSR and pack prices for representative formulations were identified from the BNF.[39] The analysis then assumed that the cost associated with each treatment would be applied for the full year and subsequently weighted based on the proportion of patients that received each medication, resulting in an annual cost of £51.29. Gross et al. 2018 reported that during the observation period, as PNs grew faster each year, 67.5% patients required increasing pain medication.[13] As such, in the BSC arm where PNs are expected to increase in volume, as shown in the Natural History study, the estimated pain medication costs are assumed to increase by 67.5% to £85.91 per annum.

Treatments for the respective AEs were identified and product prices informed by the BNF (Table 27).[39]

Table 27. Cost of adverse events with selumetinib

Adverse event	Treatment	Estimated cost per event	Proportion of patients experience AE
Diarrhoea	Loperamide (Various doses – assumed a single pack would resolve symptoms. 2mg, 30 tablets at £1.58 per pack)	£1.84	[redacted]
Vomiting	Ondansetron (4mg, two times per day for up to 5 days– 10 tablets at £1.07 per pack)	£1.07	[redacted]
Pyrexia (Fever)	N/A	N/A	[redacted]
Hypoxia	N/A	N/A	[redacted]
Paronychia	Flucloxacillin (250 mg four times a day for 7 days – 28 caps at £1.72 per pack)	£37.71	[redacted]
Dermatitis acneiform	Metronidazole cream (Typical duration of symptoms was 4 months, assume one 40mg unit would be sufficient for 1 month treatment. 40g of, 7.5 mg metronidazole per gram, at £9.88 per unit)	£3.44	[redacted]
Weighted average cost of adverse events per patient		**£[redacted]**	

Abbreviations: N/A: not applicable.
Source: BNF;[39] AstraZeneca Data on File (90DSU).[14]

The costs of pain medication and AEs can be considered small relative to the cost of selumetinib and so the inclusion/exclusion had minimal impact on the final ICER. As noted in response to Question B14d, the cost for these PN-associated morbidities have been conservatively excluded from the analysis.

c) General disease management and monitoring costs

The analysis assumes that all health care resource use costs in relation to general disease management and monitoring will be the same in both arms of the model and therefore cancel each other out. As selumetinib has a significant impact on PN volume, these patients may require fewer visits to manage their disease and symptoms. However, there is no specific data to support the quantitative difference in the symptom management costs between the two treatment arms (with the exception of pain medication costs). Therefore, for simplicity and to avoid unnecessary uncertainty, the majority of such costs have been excluded from the analysis.

Some experts noted that patients receiving selumetinib may require additional monitoring to determine treatment efficacy (tumour volume reduction/stabilisation) and potential side effects while also reducing some additional treatments, especially

pain medications. This monitoring may include MRI and while the expected monitoring frequency varied between clinicians, it was anticipated to be 6-monthly as a minimum. We have therefore included the cost of two additional MRIs per annum for patients receiving selumetinib.

d) Costs of established clinical management for PN-associated morbidities

The costs for these PN-associated morbidities have been conservatively excluded from the analysis. Due to the significant heterogeneity in PN-associated morbidities and the associated symptomatic management, it was not possible to estimate a robust cost for the associated clinical management, nor was it possible to estimate a relative reduction that may be realised with selumetinib treatment. It is assumed that the PN-associated morbidity costs would likely be reduced as PN volume is reduced and/or stabilised with selumetinib but with no means to quantify this, such costs were conservatively excluded. The only exception to this is pain costs, where a relative reduction could be estimated; this is detailed further in response to Question B14e.

e) Symptom management costs

As noted above in response to Question B14d, these costs have been excluded. The only exception is the inclusion of costs for pain medications (as detailed in Section B12.3.5 of the submission) as these were the only costs that were deemed to be quantifiable. However, the relative differences are small compared to the cost of selumetinib and inclusion/exclusion had minimal impact on the ICER.

Cost effectiveness analyses

B15. Priority question. Please explain in detail how to run the scenarios where the starting age at baseline was changed (not only the scenario analyses but also the deterministic sensitivity analysis (DSA) and especially the probabilistic sensitivity analysis (PSA)). It is clear that not only the age parameter has to be changed.

As noted in response to Question B14a, baseline age and BSA can be entered manually, the BSA can alternatively also be estimated from the age of the patient using linear regression (see Section 12.3.5 of the submission). For the scenario analysis, it is important to amend the model to ensure that the linear regression is switched on to ensure that the drug costs (which are based on BSA) are appropriately reflected.

This produces some counter intuitive results e.g. when entry age is changed (in the current version of the model) – the ICER without caregiver utilities goes up (modifying mean age on the SPRINT tab in the model to

7 years from 10 years, changes the ICER to £145,133 from £132,348) whereas the ICER with caregiver utilities goes down (£93,669 to £92,295).

a) **Please explain whether such a result is plausible or how to create scenarios which reflect plausible results.**

b) **Please also comment on the results on Table D21: these seem to suggest that the later treatment starts, the more cost effective it becomes. We also consider this highly counterintuitive.**

c) **Section 12.5.16 of the CS (page 207): A clinical expert suggested that "*starting treatment very early is unlikely to occur in clinical practice due to multiple practical reasons, including the likely inability to swallow capsules at a young age (<7 years), the time needed for PN to develop to become symptomatic (and to be deemed inoperable)*". Based on this, please conduct a scenario where the starting age in the model is 7 years.**

a) Plausibility of age-based scenarios

It appears that in the described scenarios the age was changed to seven years, however, the corresponding BSA estimate was not changed accordingly. Please note in this regard that there is a toggle on the SPRINT tab within the model spreadsheet to estimate BSA using the linear regression. As a consequence, the described scenarios were producing counterintuitive results.

We have reproduced the outlined scenarios, while also utilising the linear regression to estimate the variable BSA (Table 28 to Table 31). Reducing the age of the patients results in lower treatment costs, as dosing is based on BSA which itself is correlated to age; this is accompanied by a small QALY increase. Excluding the parent/carer disutility will increase the ICER; in the base case it is assumed that the impact on parents/carers will persist until the patient reaches 18 years of age, therefore the relative impact on parents/carers in the younger cohort will be slightly higher.

Table 28. Base case: Base line age 10 years, BSA entered manually, inc. caregiver utilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)

BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	£93,169

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table 29. Base line age 10, BSA estimated from linear regression, excluding caregiver utilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table 30. Base line age 7, BSA estimated from linear regression, including caregiver utilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Table 31. Base line age 7, BSA estimated from linear regression, excluding caregiver utilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

b) Age at baseline-related scenarios

The results presented in Table D21 of the submission appear to have been produced in error; please find the corrected results below (Table 32).

Table 32. Scenario analysis – age at baseline (Revised)

Starting age (years)	Incremental costs (£)	Incremental QALYs	ICER
5	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

c) Scenario based on a starting age of seven years

Please refer to the above response to Question B15a.

B16. Priority question. There are no scenarios on PFS and this seems to be a quite crucial parameter. Please conduct scenario analyses where the impact of changes in PFS on the model results are tested.

The impact of PFS was included in both PSA and deterministic sensitivity analysis (DSA) and was identified as one of the top ten drivers of uncertainty in the DSA. The analysis, presented in Table D19 of the submission, considers a confidence interval of 5.84% to 26.16% by Year 3, with the base case including 16% progression by Year 3. At the lower bound the ICER decreases to [redacted] per QALY and increases to [redacted] per QALY at the upper bound (Table 33).

Table 33. ICER change based on PFS variation

Variable (lower bound to upper bound)	ICER with lower bound	ICER with upper bound
Cumulative probability of progression (5.84% to 26.16%; base case 16.00%)	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio.

B17. Please answer the following questions regarding the PSA:

a) Please clarify whether the parameters of the Weibull distribution as defined in Table D15 are sampled independently in the PSA. Note that these two parameters are correlated, therefore, sampling them independently would be incorrect. Additionally, please note that to the best of our knowledge, Cholesky is not a probability distribution.

b) Please clarify whether the coefficients of the utility equation as defined in Table D15 are sampled independently in the PSA. Note that these coefficients are correlated, therefore, sampling them independently would be incorrect.

c) Please clarify whether the coefficients of the BSA equation as defined in Table D15 are sampled independently in the PSA. Note that these coefficients are correlated, therefore, sampling them independently would be incorrect.

a) PSA sampling of Weibull parameters

The parameters for the Weibull distribution are sampled using the variance-covariance matrix for the parametric model coefficients. The correlation between the variables is preserved and the coefficients are not varied independently; a Cholesky decomposition was used to implement this in the PSA.

b) PSA sampling of utility equation coefficients

Previous attempts were made to contact the authors of the Ara and Brazier 2010 publication[45] to provide the associated variance/covariance matrices, however these have been unsuccessful. As such, we have been unable to model the correlation and the samples have been varied independently, however, we do not believe the impact of this to be significant. One potential solution would be to exclude the age-related disutility from the PSA (i.e. keep it fully deterministic) as this would remove any of the erroneous variance that sampling the coefficients independently would create.

c) PSA sampling of BSA equation coefficients

We do acknowledge that these coefficients are likely to be correlated but there is a very limited dataset available to determine the correlation and therefore we suggest that a potential solution could be to exclude these coefficients from the PSA.

Model validation

B18. Priority question. Section 12.7.1 of the CS provides insufficient details about what validation efforts were performed on the model and what the results of these validation efforts were, e.g. how the parametric models fitted to TTD data from the SPRINT study were validated or the explicit feedback from clinical experts regarding various modelling aspects. These additional details could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/).

Please confirm also whether black-box tests to detect modelling errors were conducted. If not, please conduct these tests as well and provide an overview of their results. Black-box tests could be conducted for example (but not necessarily) with the help of the verification tool TECH-VER (DOI: https://doi.org/10.1007/s40273-019-00844-y).

During development, the model underwent interim quality check by the model developers, and a senior health economic modeller that was not involved in the model development performed quality assurance. Whilst we did not originally use the TECH-VER checklist, we did perform an internal validation which did include a range of black box tests that are closely aligned to those suggested in the TECH-VER checklist. However, in response to the request we have now completed the TECH-VER checklist (see below).

TechVER_Checklist.xlsx

For initial clinical validation, relevant methods and assumption were presented to four clinical experts from across Europe, including one clinician from the UK; these included: the model structure, residual benefit post discontinuation, key cost, utility and clinical assumptions (including use of parametric models fitted to TTD). All of the clinicians felt that data used and the pragmatic assumptions were reasonable. As a result of this initial validation, the additional costs for MRI scans were included to assess the clinical response for those patients receiving selumetinib.

Following model development, in-depth UK validation was carried out to ensure that the modelling was appropriate and applicable to the UK setting (see Section 10.6.2 of the initial company submission). A total of four clinical experts were consulted, with 1-hour teleconferences, carried out in July 2021.[1] The clinical experts, all currently involved in the management of paediatric NF1, comprised of two paediatric oncologists, one lead nurse, and one geneticist; the latter two experts are involved in 'lifespan' service and see both children and adults with NF1 PN. The clinical experts were selected on the basis that they were all based in England and had direct experience of treating patients with NF1 PN. All of the experts had direct experience of selumetinib use in their centre. Feedback was obtained via structured interviews including questions on the following topics:

- The clinical course of symptomatic inoperable NF1 PN and the current clinical pathway for patients
- Comparability of the SPRINT study population with UK setting
- The clinical benefit of selumetinib and any safety/tolerability considerations
- Wider aspects of care for patients, parents and carers
- The link between the disease course of NF1 PN and HRQoL over time, and the potential impact selumetinib as incorporated in the economic model

From the UK validation study there was general consensus that:

- Under current clinical management without selumetinib, the HRQoL of patients with NF1 PN is low for both children and adults
- The HRQoL of patients treated with selumetinib will be higher than those receiving only current clinical management
- Some patients receiving selumetinib will experience reduced or stabilised PN growth; this results in an optimal/peak HRQoL value
- Some patients receiving selumetinib could still experience disease progression (PN growth ≥ 20%) at some point; this would have a negative impact on HRQoL
- There are reasons to believe that selumetinib could continue to benefit patients after treatment discontinuation: the benefit of starting treatment in the paediatric setting is preventative in nature, and that the intention would be to intervene to limit the impact of NF1 PN on the patient as early as possible
- Selumetinib will form an effective preventative therapy for patients whose PN would otherwise grow and persist into adulthood, with associated disease burden

Electronic model

B19. Priority question: Please answer the following questions regarding the electronic model:

a) **On the SPRINT worksheet, please explain the differences between the two approaches used to calculate body surface area (BSA).**

b) **On the model inputs worksheet, please explain whether the method by Ara and Brazier is also applied to patients under 16 years. Please include in the model the option to select the age at which the age-decrement utility starts to apply.**

c) **On the caregiverUtility worksheet, please explain the difference between the two options implemented to calculate caregiver QALYs (Proportion change and Absolute reduction).**

d) **On the results worksheet, please note that LYG should be discounted as well.**

e) **On the _Scenarios worksheet there are some #REF! errors. Please correct them.**

a) Different BSA calculation approaches

"BSA from SPRINT" allows the user to enter a baseline BSA at point of entry into the model; BSA then increases year on year adding the age coefficient defined on the BSA_PopUp tab.

"BSA calculated using linear regression" simply uses the linear regression to estimate BSA from point of entry, utilising the age at baseline.

This results in slight differences in BSA estimates for patients starting at ten years of age, between the manually entered BSA aligned with SPRINT and estimating BSA via the linear regression alone.

b) Application of Ara and Brazier

As noted in response to Question B12, the inclusion of the Ara and Brazier algorithm can be considered conservative and can also be deactivated within the model. In a scenario analysis, removing the Ara and Brazier algorithm[45] results in an ICER of [redacted] per QALY (compared to the baseline ICER of £93,169 per QALY; Table 34).

Table 34. Scenario analysis – excluding the Ara and Brazier 2010 utility adjustment

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

c) Difference between the two options implemented to calculate parent/carer QALYs

As noted in the response to Question B8b, the model allows for the impact on parents/carers to be estimated as a proportion change aligned with the scale of impact seen on the patient, or as an absolute reduction.

In both approaches, an age-adjusted utility value is estimated for the parent/carer, assuming a mean age of parents of 30.6 years at childbirth based on ONS statistics,

and a general population utility value is determined using the regression algorithm from Ara and Brazier 2010.

For the proportional change approach, the mean relative difference in utility between the selumetinib and current clinical management patient cohorts is calculated; this is then used to weight and calculate the associated parent/carer utilities in the BSC arm.

For the absolute reduction approach, the figure entered into the model is deducted from parent/carer's general population utility in the BSC arm.

d) Discounting of life years gained

Discounting of life years does not appear to be intuitive in terms of how life years are used in the model. The use of undiscounted life years is useful because it allows for simple interpretation of results and for the calculation of mean time to events if needed; discounting life years would make these calculations less objective. Discounting is considered for QALYs, and by extension the ICER, due to the incorporation of utilities.

e) Errors in the Scenarios worksheet

Thank you very much for flagging; we can confirm that this has been resolved as part of the revised model.

Section C: Textual clarification and additional points

C1. Regarding the marketing authorisation:

a) Please provide an update on the current status of Medicines and Healthcare products Regulatory Agency marketing authorisation [redacted].

Selumetinib was approved by the Medicines and Healthcare products Regulatory Agency in August 2021.

b) Please confirm whether the date should be marked as in-confidence. In the executive summary the information is not marked while in section 3 the information is marked as in-confidence.

We can confirm that this information no longer needs to be marked as commercial in confidence.

C2. Section 18 of the CS ("Related procedures for evidence submission") contains NICE guidance included in the submission template.

Please confirm that no text intended to be included is missing from the CS.

We can confirm that no text intended to be included is missing from the submission document; this includes Section 18, where guidance text from the initial NICE template can also be removed if preferred.

C3. Page 43 of the CS: disfigurement is not included in Figure B4. Please explain the importance of this morbidity.

While not formally included as a separate morbidity in the Gross et al. 2018 study (which provided the basis for Figure B4),[13] disfigurement due to PN can be severe and can result in a substantial impact on the quality of life of patients of any age (as detailed in Section 7.1 of the submission); disfigurement due to facial PN in particular can also contribute to functional morbidities such as vision loss (as detailed in Section 6.1 of the submission).

C4. Caption of Table D18 seems incorrect. Please check and correct, if needed.

Thank you for flagging; we can confirm that this caption is incorrect and should instead read as follows: **Table D18. Overview of cost results by category**

C5. Table D16: Life years gained (LYG) should be discounted as well.

Please refer to the response to Question B19d.

C6. Regression coefficients in Figure D5 do not match with those reported in Table D12. Please check and correct, if needed.

We can confirm that the regression coefficient values presented in Table D12 of the submission document are correct; please find a correspondingly adjusted version of Figure D5 below.

Figure D5. Fit of linear regression to BSA data over time from SPRINT

Abbreviations: BSA: body surface area.

C7. Please clarify what the time period in Tables C16 and C17 is. For example, ORR = 68% but it is not clear after how many years. Also, duration of response is 8 cycles, but it is not clear what constitutes a cycle in this context.

The tumour volumetric outcomes reported for SPRINT Phase II Stratum I and the Natural History study refer to a time period of three years (corresponding to the median duration of follow-up of 36 cycles as reported in Gross et al. 2020).[5]

The term "cycle" in this context refers to selumetinib treatment cycles (with each cycle being one month [i.e. 30 days] long; also see Table C5 in the submission document).

C8. States in Table C36 seem to be mixed. Please check and correct, if needed.

Please find below a corrected version of Table C36 where the utility values are assigned to the appropriate states.

Table C36. Summary of HRQoL values for cost-effectiveness analysis

State	Utility value	Confidence interval	Justification
Paediatric patient without selumetinib	[redacted]	[redacted]	In the absence of suitable utilities from clinical trials or the published literature, a de novo analysis TTO study was considered appropriate
Paediatric patient with selumetinib	[redacted]	[redacted]	

C9. Please explain the shapes observed in Figure D6.

The initial uptick in utility is attributable to patients receiving and benefiting from selumetinib. Over the next eight model cycles, a proportion of patients will progress and so the associated HRQoL for patients on treatment decreases while the HRQoL for those off treatment increases. This is in addition to the Ara and Brazier 2010[45] age adjustment and mortality; after this point onward (8 model cycles) the data reflect only the Ara and Brazier age adjustment and mortality. Please note that in the base case, no differential mortality is considered within the analysis.

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Appendix A: TTO Vignette Study

Please double-click on the below icon to open the TTO Vignette Study report in a separate Word document:

TTO Vignette Study.docx

NICE National Institute for Health and Care Excellence

Patient organisation submission

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 Neurofibromatosis in children aged 3 years and over.

Childhood Tumour Trust Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Childhood Tumour Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	When your child is diagnosed with an incurable medical condition; your entire world is turned upside down! As a parent/carer you leave the hospital/doctors with your head in a whirl. Having a child who is diagnosed with any medical condition is hard to understand and deal with, but when your child has a diagnosis that very few people have heard of (including a lot of medical professionals) or can even pronounce seems to make it harder to take in and try to begin to understand. Those who are diagnosed with Neurofibromatosis (NF1) and their families are left googling what it means, there are few support groups and little support outside the specialists who know what NF is. Childhood Tumour Trust let you know you are not alone. We encourage families to meet and just talk about everything you need to talk about, with people who understand and can relate to the endless appointments, treatments and how you feel. We aim to link people together not just in the UK but all over the world. We want to organise special days out by providing tickets to various attractions around the country so families can spend a day together away from hospital appointments and day to day living with the condition We have produced a Health sketch and a CPD module for health care professionals and are currently designing a CPD module for Educational Psychologists. We currently have in excess of 1.8k parents/carers and families who are active members of our online support group and support many more children and young people via our online groups and workshops, days out and camps. We have a very active medical board and our own educational advisor on hand to support our members. Our charity is funded solely by fundraising and specialist grants.

4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Charity supports over 1.8k families, support is given via a Facebook group, Facebook page, website and group get togethers as well as virtual sign language, baking, art and singing groups for our children and young people. We also host counselling sessions for parents and carers. As well as a medical board and an educational advocate, [redacted] works closely with individual families, schools and professionals involved in each child's care, as well as providing information on the SEND system to all of our families via social media and our website. We work closely with all our families and offer support guidance and opportunities to discuss life with NF, parents, Carers, children/young people and adults share their experiences of living with Neurofibromatosis and the impact upon activities of daily living, education, Heath and the support or lack of support they feel they have from health , education. Views are gathered with consent of all individuals. Other views used in this application are from our lives experiences as parents of children with Neurofibromatosis and [redacted] experiences of living with the condition, as well as experience as a paediatric nurse for 15years, [redacted] experiences of running the charity and working closely with medics and other professionals who specialise in NF.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a person living with the condition it is very difficult as you do not know how you will be affected and what to expect long term, Neurofibromatosis can affect every aspect of your life from schooling and education –making friends- getting a job- being independent- starting a family-and long term life goals .. it can mean you have additional co-morbid conditions such as learning disabilities, autism, adhd or mental health problems or severe physical impact affecting mobility(such as hyper mobility , poor muscle tone or even scoliosis, bone deformity, amputation), disfigurement/appearance, causing significant pain.. NF is different for each and every person and is very unpredictable which

	makes managing it and living with it even harder, the care received varies depending on postcode or whether you are under a specialist centre and for some young people who we support (18-30) and other adults there is no one who manages their health care following discharge from paediatric services despite them having a more complex form of NF, also their GPS are not trained in Neurofibromatosis so are unable to support them or easily dismiss problems that turn out to be serious complications. For parents and carers of a child/young people with NF especially those where the child is the first in the family with NF it is a scary journey where many feel unsupported by the NHS, Schools and other services. Sadly despite a lot of work that has taken place through the Childhood Tumour Trust diagnosis is often late and there is missed opportunity for early intervention and involvement of appropriate professionals for treatments and therapies meaning optic pathway glioma are missed and diagnosed at a point where sight loss has already taken place, plexiform fibroma are misdiagnosed, and sometimes it is not until a patient reaches a sarcoma clinic that they are told they have NF1, or in some cases 'lumps' are dismissed as just part of NF and turn out to be sarcomas, help and support needed in education is not given, therapies such as Speech and language and occupational therapy is delayed.. This can all have a huge detrimental effect on these children/YP and their families/carers. Families and carers have stated how alone they felt prior to finding CTT and how much our help, support and information has helped them to cope both pre and post diagnosis. Sadly as a parent of 2 children with NF [redacted] has personally experienced the constant fight to get the correct treatment and support for her children, as a parent she feels that she is not always listened to by health care professionals, education and social care and has had to fight extensively to get her children the care, support and education they need despite their diagnosis of NF from 6 weeks old the children have not received the date they should without a battle, this for us as a charity is very concerning as not all parents will know to fight or what to fight for and not all of the parents or Carers will be able to do that for their children as some will have learning disabilities/difficulties themselves or will have had bad experiences themselves as a child/young people with NF. [redacted] has fought tirelessly for years for Early Diagnosis including designing body maps for child health records and getting them published and in many red books across the country, Changes to Care Pathways and for research into NFall while bringing up her daughter who has NF and going through her daughters diagnosis and years of treatments and hospital care

	NF can be very scary. It's unpredictable therefore you are constantly dealing with the unknown. There needs to be more support and help for those with NF and those caring for people with NF as well as a very clear care pathway and more training for medical professionals and education and social care.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The treatment options currently available are limited and can depend on where you live. There is not a standard for NF care across the NHS and a new care pathway is needed to ensure equal care for all Parents are being told … "nothing can be done", "it's part if having nf and the children have to learn to live with it", "we can remove part of the plexi not all of it .. and it's likely to grow back" , "no treatment is available" , "it's not that bad.. we wouldn' t treat that" Parents feel that often there is no option for their child/YP. Treatment options on the NHS are dated and despite the progress being made in the medical world things in the NHS haven't moved on for the treatment of NF. "Invasive therapies aren't appropriate for younger children when there are new technologies available and NHS treatment should reflect this." "People with NF should not be told to just deal with it, it's part of having NF this is not appropriate in 2021".
8. Is there an unmet need for patients with this condition?	Currently the treatment options are very limited, this is due to the options available and when they can be used. Chemotherapy carries its own risks. Radiotherapy should not be used in patients with nf unless it's a last resort due to the high risk associated with radiation and NF.

	Surgical removal of plexiform neurofibromas is very complex and they often cannot be fully removed so there is a high chance of regrowth as well as a high risk of nerve damage. Many people with painful plexiform fibroma have no relief and although they can be surgically removed this is often refused by primary care DRs who see it as a cosmetic procedure and carries the risk of regrowth, scarring and infection. Pain relief often takes a considerable amount of time to get right, nerve pain is very difficult to manage especially in children and young people. the availability of pain management clinics for children and young people is very limited meaning that pain management can be very poor, this has a knock on impact upon quality of life and on all aspects of daily living, often children and young people with NF will have to take a number of days off school for medical appointments, this will be dramatically increased for a child with poorly managed pain. The proposed treatment could over time drastically improve pain management for individuals with Plexiform fibroma's and reduce the knock on impact upon their day to day life. Children with NF often have difficulties in school and fall behind their peers, those who have to have numerous invasive treatments for plexiform fibromas or whom suffer pain or disfigurement will be more at risk that their peers with NF and are more likely to require additional support in school due to lost time due to appointments/pain/treatment, social and societal impact of having a plexiform tumors especially with disfigurement and the emotional and mental health implications of their diagnosis. A treatment is needed that is non invasive which carries lower risk of complications and long term effects That is available to all who fit the criteria rather than those who attend certain hospitals.

Advantages of the technology	
I	Non invasive/Non surgical treatment. Can be used to treat inoperable plexiform neurofibromas. Less impact upon quality of life compared to conventional treatment. Improvement of quality of life for patients with NF and plexiform Neurofibromas. No repeated surgical treatment. Less impact on a child/YP development and education. Reduced pain and reduced need for long term pain medication Reduced impact on the patients mental health Easier for the patients family to manage Long term improvement on quality of life
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	New treatments are not available to everyone. It feels very much like there is a postcode lottery, unless you are cared for by a specialist or fight for certain treatments the treatment options are reduced greatly. Knowledge of treatment is not widespread. Cost implications - will local CCG's fund these treatments or will it only be available in certain areas or to those who attend specialist centres. Studies over time- what are the long term impacts of the drug looking 20-40yrs into the future?

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not all patients with NF have plexiform Neurofibroma so those with this diagnosis will benefit more from the technology. Though over time it may be beneficial for more if it is approved for treatment of other types of fibroma. Patients who have a plexiform that impacts a major structure/causes mobility or functionality difficulties/severe disfigurement (though this is subjective to each individual) may feel that they will benefit more from this than someone with a plexiform that does not cause them issues on a daily basis. It is very important to keep in mind this is subjective and each patient will have a different view on the benefit they would receive from this treatment. Patients who have been able to have partial surgical treatment such as a resection for their plexiform may not feel that they would benefit as much from this treatment though this will depend greatly on the results of the surgery and if the tumour returns quickly or becomes larger than it was pre operatively. Age and medical history/general health may factor into the decision also, NF can be impacted by hormonal changes so it would need to be looked at whether it is more effective to treat following puberty for a child in their adolescence or to treat before and /or during puberty to limit growth. Ethnic background/religious beliefs/ethical beliefs may impact uptake of treatment.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Treatment needs to be available to everyone, therefore there needs to be training in more hospitals so that the care is equal whether you are seen at your local district hospital or a specialist centre. There needs to be more information available to patients and their families so an informed choice can be made about treatment options. Social divide needs to be considered, families affected by NF come from a wide range of backgrounds, treatment offered needs to be equal and should not be based on a person's knowledge, understanding or by their beliefs or religious or ethnic background … treatment should be offered and should not need to be sought out by the patient or their family, consideration needs to be given to individual beliefs but patients should not be ruled out on this basis. Patients who cannot access the specialist centres should be able to access the treatment. The use of the treatment should be based on need, there needs to be clear guidance for CCGs to ensure that patients who need the treatment aren't denied on a cost basis - no postcode lottery. Each patient needs to be assessed individually to see how they are personally affected by their condition- the criteria should not be solely based on size/position/number of structures affected but also the emotional/mental health impact upon the patient.
Other issues	
13. Are there any other issues that you would like the committee to consider?	A baseline MRI in a young child should be done followed by one in early adulthood. a plexiform neurofibroma is present from birth, therefore if there is not one present as a young child one will not develop. This way plexiform fibromas will be identified early on and hopefully before any major complications, this is especially important as not all plexiform tumours are visible on the outside.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- As an organisation we support the target group of patients specifically from birth-30 along with their parents/carers and family.
- We have personal, professional and lived experiences of the condition/caring for those with the condition so can give a rounded perspective on the condition and treatments.
- We have personal and professional experiences of the treatment/lack of treatment of plexiform Neurofibromas and have a large number of members who have shared their experiences and are happy for us to use these to guide and support this process.
- As an organisation we have the collective experience of thousands of members we will be speaking on behalf of them as well as sharing personal experiences of living with the condition and caring for those with the condition, we have the unique ability to offer perspective from lay people (those unaffected by NF), Children and Young people with NF, Adults with NF, Carers for child with NF (some of whom equally do not have or do have NF themselves), experience from medical and other NHS professionals as well as experience for a educational and social care standpoint.
- We feel it important to see the patient as a whole and the overall impact having a plexiform has on their day to day life .. we want to ensure that the individual affected by Neurofibromatosis is seen and not just a diagnosis or number.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

[redacted] Childhood Tumour Trust August 2021

Your privacy

The information that you provide on this form will be used to contact you about the topic(s) above.

X☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: BPNA
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many patients would be expected to be eligible to take selumetinib in England?

Within the combined highly specialised service for children with complex NF (Manchester and London), we see on average 150 pts per year with symptomatic plexiform neurofibroma (PN). Of these we anticipate that 5-10 pts per year will be eligible to receive Selumetinib

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Children with NF1 and symptomatic plexiform neurofibroma (PN) are managed within the nationally commissioned services- Manchester and London and we accept referrals from all over the UK. We have agreed national protocols and standards of care. At present there are 3 main treatment pathways for children with symptomatic PN: conservative (which includes pain management), surgical and medical treatments; MEK inhibitors (MEKi). We set up a national MEKi MDT in 2017 and hold meetings 3 x per year to discuss treatment options and eligibility for MEKi. There is varied and in some places scant knowledge outside of the national service on treatment options for children with complex NF1 plexiform neurofibroma.

Evidence from trials performed in the US at the National cancer Institute ('Selumetinib in children with inoperable plexiform neurofibroma' BC Widemann et al NEJM March 2020) suggest PN partial volume reduction on imaging (MRI) of around 20% in 70% of patients treated and some clinical benefit in those experiencing pain symptoms and some improvements in strength and motor function in those who were assessed however we as a group believe that data is lacking with regards to overall convincing objective clinical improvement due to small numbers of patients evaluated, clinical heterogeneity (PN in different locations cause different symptoms) possible placebo effect as no other medical therapy is available and no comparable control group studied in clinical trial. The positive effects on pain symptoms and improvement of motor function reported in the NCI trial may be because MEKi changes the texture of plexiform neurofibromas making them softer.

There is a study currently underway in London of Selumetinib to evaluate this further (INSPECT trial).

In the UK we have seen stability of growth in young children with potentially life threatening PN treated with MEKi and we believe this group of children may be the ones to benefit most from treatment. These children are taking a paediatric formulation of MEKi –Trametinib (Novartis). Unfortunately

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Selumetinib is only available as a tablet preparation and therefore not suitable for very young children.

Other disadvantages of treatment are the frequent hospital visits required (certainly initially) to monitor for side effects including blood tests, ECG, eye tests, significant skin toxicity and in younger children nail bed infections. The other unanswered question is when to stop treatment as PN grow throughout childhood so there are additionally significant cost implications.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There are patients with NF1 who are more at risk of developing malignant peripheral nerve sheath tumours (malignant transformation of a PN) and Selumetinib would not be appropriate for these patients. We do not know at present which children are most likely to benefit.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?
Yes. At 2 levels:

1. ***Increase in number of children referred for consideration of MEKi which involves a clinical review, review of imaging in a radiology MDT, obtaining a surgical opinion and discussion in relevant surgical MDT. Once these have taken place children are then discussed in our MEKi MDT***
2. ***If the MDT agrees that MEKi is the best treatment option then we anticipate that this will be delivered and monitored in designated local oncology units pending their agreement. This will require blood tests, cardiology and ophthalmology assessments as well as completion of clinical outcome measures, The latter involves multiple teams as is dependent on the location of the PN ie airway will involve respiratory assessments, eyelid plexiforms will involve visual assessments etc..***

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Yes MEKi are available both via compassionate access programmes and clinical trials–currently for our patients these are accessed via the nationally commissioned NF1 service

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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The nationally commissioned NF service follow standard clinical guidelines for monitoring of NF1 (RE Ferner Journal Medical Genetics 2007 'Guidelines for the diagnosis and management of individuals with NF1') which are currently being updated. These follow European guidelines. Monitoring of individual complications (namely optic pathway glioma, brain glioma and plexiform neurofibroma) is by and large standardised amongst the international NF community. We have eligibility criteria for consideration of MEKi as per those used in the initial NCI trials. We feel strongly that all NF1 children with symptomatic PN should be seen within the national service and decisions with regards to MEKi be made in our national MEKi meeting as is current practice. The reason being that children will benefit from the expertise of the multidisciplinary team. They may otherwise be denied other more suitable treatment options eg surgery or be subjected to a potentially harmful treatment that they are unlikely to benefit from. This therefore requires careful evaluation within the expert MDT.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
There is no current alternative medical treatment for inoperable PN in children. Some children may be eligible for surgery within expert teams.

Yes more frequent clinical assessments and monitoring will be required

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

As a group of clinicians managing children with complex NF1, we firmly believe that all children with NF1 PN who are being considered for treatment with a MEKi should be evaluated within the highly specialised nationally commissioned NF1 service. This should include not only decisions to start but also assessment of response and when to pause and stop treatment.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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1. ***Patients selected for the NCI MEKi trial will differ slightly from the patients discussed in our MEKi MDT for 2 main reasons:***

i) ***By definition they have already had an expert surgical opinion and are deemed 'inoperable'. Our current practice is to discuss all potentially eligible patients within an MDT which will include in some cases a further surgical opinion which may differ to the one sought prior to referral,***

ii) ***Patients in NCI trial are a selected group of patients who were generally more symptomatic from their plexiform neurofibromas than we see in our complex NF1 clinics. This is what would be expected in patients enrolled in a clinical trial vs patients seen within a clinical setting. However we would imagine that the patients we then put forward for MEKi would reflect the types of patients taking part in the NCI trial.***

2. ***The outcome measures used in the NCI trial are similar to those adopted in the current INSPECT Selumetinib trial in London and we would anticipate drawing up similar but simplified outcome measures for clinical practice. It may not be feasible to complete all of these within the NF clinical setting (due to heterogeneity of location of PN requiring involvement of multiple specialist teams)***

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Main side effects are skin toxicity and nail bed infections. Other side effects may come to light as we get more information from the INSPECT trial

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

We would strongly advocate that delivery of care should be via the existing national service framework so our current pathway to determine eligibility would remain. The numbers of patients discussed would inevitably increase resulting in requirement for additional clinician/ nursing/ admin time.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which selumetinib will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Children who are not known to / referred to the national NF1 service will not be aware of treatment options and could therefore be disadvantaged although knowledge of NF1 is increasing amongst GP's via the work done by the NF charities.

There may be an issue if once eligibility is agreed children are not easily able to access treatment via their local oncology centre and have to travel

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Topic specific questions

What is the relationship between reducing the tumour volume and heath related quality of life in people with symptomatic and inoperable plexiform neurofibromas?
In the NCI phase 2 study (quoted above) there was no correlation between reducing tumour volume and clinical improvement

How frequently do plexiform neurofibromas develop into malignant peripheral nerve sheath tumours?
In children this is around 1%. Lifetime risk is between 5-15%

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NHS organisation submission (CCG and NHS England)

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHS England clinical commissioning policies for neurofibromatosis type 1.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined for this patient group and there are no significant differences of opinion between the professionals
8. What impact would the technology have on the current pathway of care?	The technology will provide a new treatment option for patients; surgery is currently the only option and may not be feasible in some cases due to tumour size and location.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	The technology is not currently routinely commissioned.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be administered through existing commissioning arrangements
• How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option where the only current option is surgery.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be initiated by the two commissioned specialist centres that deliver services for patients with complex neurofibromatosis type 1.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None – as treatment is in tablet form
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	These will be developed as necessary

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	As it is not routinely commissioned, there are no current evaluations or audits.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
12b. Consider whether these issues are different from issues with current care and why.	None

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Karine Lascelles**
2. Name of organisation	**Evelina Children's Hospital, Guys Neurofibromatosis Service, Guys and St Thomas' NHS Trust**

3. Job title or position	**Consultant paediatric Neurologist. Paediatric lead for NF1/ 2 Service**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x**☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stop progression / improve function/ reduce disfigurement
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinical outcome measures are more important that radiological volume reduction. This is difficult to evaluate due to the fact that plexiform neurofibromas are heterogeneous and occur in different locations
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Answered in previous HST appraisal document
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Answered in previous HST appraisal document
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Answered in previous HST appraisal document
• What impact would the technology have on the current pathway of care?	Answered in previous HST appraisal document
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Answered in previous HST appraisal document

• How does healthcare resource use differ between the technology and current care?	Answered in previous HST appraisal document
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Answered in previous HST appraisal document
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Answered in previous HST appraisal document
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Answered in previous HST appraisal document
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	No
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As yet unknown but as a group treating NF PN pts we believe that the younger patients with extensive disease burden may have the most to gain from selumetinib although the treatment is not currently available in a paediatric suspension (tablets only)
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Answered in previous HST appraisal document

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Answered in previous HST appraisal document
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Answered in previous HST appraisal document
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Answered in previous HST appraisal document. Skin toxicity, nail bed infections. Burden of hospital visits in light of monitoring required (cardiac examinations, ophthalmological examinations, blood tests, scans)
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	UK clinical trial; INSPECT study is underway and will hopefully answer question
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Answered in previous HST appraisal document
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Answered in previous HST appraisal document
22b. Consider whether these issues are different from issues with current care and why.	Answered in previous HST appraisal document
Topic specific questions	
23. Are age, plexiform neurofibroma (PN) volume and	Age yes due to lack of paediatric formulation available currently

PN location expected to be treatment effect modifiers?"	
24. Do patients receiving current treatment all have progressive disease or can some patients stablise for a period, before their disease progresses?	Not all have progressive disease, some are stable
25. After 18 years of age does the tumour size plateau? Would a patient then experience no further disease progression?	Not necessarily – adult studies underway
26a. To better understand what costs are involved in treating patients, what are the current healthcare resources used/ medical appointments	Answered in previous HST appraisal document

attended by patients, for both a child, and as an adult?	
26b. On average how many MRI scans would a patient receiving selumetinib have per year compared to best supportive care?	As part of a clinical trial every 3 months Anticipate scans every 6 months but we have not agreed this yet as a group

Key messages

27. In up to 5 bullet points, please summarise the key messages of your statement.

- PN can be extensive, disfiguring, painful, affect function and impact on QOL
- Selumetinib is the only medical treatment that thus far that has been shown to stabilise growth on volumetric MRI
- In evaluating any treatment, clinical outcome measures should be paramount. We have some data on positive benefits but numbers of patients are small and clinical outcome measures are difficult to apply uniformly due to heterogeneous nature of PN in NF1
- The treatment is not free of side effects and both this and the burden of hospital visits should be taken into account when balancing with any potential benefit
- All children in the UK being considered for selumetinib should be referred to and discussed in the NF1 national MEK MDT to ensure eligibility including inoperability criteria are met

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Highly Specialised Technology Evaluation - Patient expert statement

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Mrs Clare Barklam**
2. Are you (please tick all that apply):	**x☐** a patient with the condition? **x☐** a carer of a patient with the condition?

	☐x a patient organisation employee or volunteer? ☐x other (please specify): experience as a paediatric nurse 15 yrs (no longer practicing)
3. Name of your nominating organisation	Childhood Tumour Trust
4. Did your nominating organisation submit a submission?	☐x yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐x yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes i co wrote the submission for CTT but please see additional comments below
7. How did you gather the information included in your statement? (please tick all that apply)	☐**x** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐**x** I have other relevant personal experience. Please specify what other experience: ☐**x** I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition?	I was diagnosed at 3yrs old , information then was incomplete and inaccurate, i have learned alot more about NF since having my children but mostly through reading journal articles and research as well as attending conferences and completing training on NF., rather than from the medics caring for my children. my children had blood tests at birth so were diagnosed at around 6 weeks of age, by this time i knew they both had nf, the dr who gave me my sons diagnosis had to search nf on google prior to the consultation-search pages were still open and he asked me what he needed to do for my son this was not very reassuring and we ended up changing hospitals.

What was the impact of this you and your family?	the impact on the children's father has never been considered by medics nor has the impact on me they always just assume because i have nf myself they dont need to explore this, we have had no support from medics through diagnosis in fact i had to fight to get my sons multiple plexiform tumours diagnosed and his brain tumour and thickening of the optic nerve, this was very scary and we still feel in limbo as no treatment has been offered. this has severely impacted my marriage to the point of possibly splitting our family
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to	please see ctt's response i personally had to give up work due to my health and the impact of my NF and my childrens nf on my mental health. i have to care for my daughter full time, she is home schooled (ASD, NF, Lymphatic malformation, dyslexia, dyspraxia, hypermobility, poor tone fatigue …… plus more) this has a huge impact on my emotional social and mental health. my son is in specialist school - nf , ADHD, Dyslexia , dycalculia, possible ASD, plexiform neurofibromas, glioma and thickening of optic nerve. i had to fight to get support in school for my children- i had to go to tribunal 3 time and a 4th was stopped at the last minute as the LA agreed with my requests for the school and provision for my son. this has caused immense stress and financial hardship as i had to get assessments as the LA assessments were inaccurate. i have no social life NF impacts me personally with my anxiety and depression, but caring for my 2 children takes up alot of my time. financially i struggle as i can no longer work as a nurse. Both children have EHCPs both struggle academically despite having average and above average IQ they are working at 2 yrs bellow expected for age and ability.

school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	NF impacts their ability to make and maintain friendships, both have social communication difficulties. my daughter is very demanding due to trauma from early hospital admissions and surgery for lymphatic malformation(- this is another condition the drug in question is used to treat) she has attachment difficulties and finds it hard to share me with her brother, this impacts my ability to help and support him, they have a very difficult relationship and clash a lot possibly due to the ASD/ADHD and their high level of need . our whole life is adapted round the children. what we eat, where wego, how we travel, having to plan and not be impulsive for one and for the other needing to change and addapt and not place any demands on her at all. due to my childrens needs i have not had more children despite wanting more as my daughter simply would not cope.we had a round of IVF PGD prior to conceiving my daughter which failed- we had no viable embryos this was hugly distressing and had a huge impact on my marriage. the not knowing what will happen with nf and when and how things could change and develop causes alot of anxiety and worry for my childrens future and myself
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	please see ctts response there is not option currently available for inoperable plexiform tumours- people are left in pain, with deformities and impact of function dependant on location. - pain services for children are very poor or non existent, adult pain clinics are difficult to access and often do not understand the pain caused by nf and plexiform tumours - some drs still think nf does not cause pain. surgery can only debulk not remove plexiform tumours, they often return and can grow larger than they were pre surgery , personally i have had 5 or more surgerys on a facial plexiform - cheek/nose and have been told its full thickness of my cheek and nose and further surgery would require full reconstruction on

	my nose using cartilage from my ear, surgery has helped me to breath and gave me symmetry back to my face but gradually my nostril is becoming blocked again and the area is sensitive and visibly growing again this is after 4yrs- it is not reasonable to expect people to have repeated surgeries in one place that do not solve the underlying issue. options are not discussed you have to fight as a adult and child to see plastics for possible surgery, other options are not discussed. sadly the answer many of us are given is “its your NF, learn to live with it” If someone else saw a DR with a large growth or a glioma further investigations would be done and treatment options given and fully explained but sadly for those with a NF diagnosis we have to fight for the right imaging to be done, referrals to the right specialists and for treatment.
11. Is there an unmet need for patients with this condition?	yes there is a lack of options for treatment of plexiform tumours and gilomas , many children are placed on multiple failing chemo protocols that have a severe impact on the childs health and families wellbeing or if surgery is deemed to be a option they many end up having multiple surgeries as the tumours reoccur and cannot be fully removed. some patients are offered no treatment and placed on watch and wait families feel in limbo and like they cannot do anything for their child. in the uk only “complex” patients are seen by the specialist nf teams so many children are never seen by someone experienced in NF so can be receiving substandard care, it is a postcode lottery to who you see and what treatments they offer. there needs to be a national care pathway for children and adults
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the	please see ctts response and comments bellow

progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	please see ctt's response. this has not been offered to myself or my child though we both have inoperable plexi's and my son has a glioma, travel would not be a issue as for the right treatment we would make the journey. though the treatment needs to be available more widely than it is currently as many families cannot travel the distances currently required.

Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	see CTT's response - we are gathering feedback to present at the meeting
Patient population	
15. Are there any groups of patients who might benefit more or less from the	please see CTT's response

treatment than others? If so, please describe them and explain why.	
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	- **postcode lottery** - **parental LD impacting ability to understand treatment and comply with treatment.** - **lack of knowledge and awareness of the treatment -parents/patients/medics** - **financial implications of travel to the hospital if not delivered by district generals** - **should not only be available to those attending complex centres**
Other issues	
17. Are there any other issues that you would like the committee to consider?	CTT-Childhood Tumour Trust support children and young people affected by Neurofibromatosis Type 1 and their families and carers. CTT was founded by Vanessa Martin whose own daughter has NF1, over the years the charity has grown significantly and now supports in excess of xxx families. The charity supports research into NF and campaigns and lobbys government for change in the care of individuals with NF1, camps for children and young people including sending members to the camp in America as well as providing support via a Facebook group, website and educational advice provided via email/Facebook or telephone. We have a medical board who help and advise us on problems that members present with meaning we can offer the best possible accurate information and guidance, we also send medics on training and fund places at medical/nf conferences and training. During lockdown the charity started to run Zoom sessions in cooking, craft, singing and sign language. This brought the children and young people together developing social skills and meeting their occupational therapy and speech and language needs as well as learning new skills in a time where many could not access school and were missing out on therapy and the social aspect of school, and because everyone joining in has NF

	or a sibling with NF they all understand each other and have no expectations or misunderstandings their peers at school may have, it has been so popular and made such a difference to our members that sessions have continued after lockdown. The charity also developed a RED book insert for children with NF detailing all of the medical check ups children need and the key things to look out for and what to do if they arise, we also have successfully introduced body maps in the red books in a number of areas in the UK so that birthmarks can be clearly documented and referrals made in a timely manner... to complement this we have developed a number of CPD modules for medical professionals to learn about NF. Clare Barklam – I initially joined CTT as a member as both myself and my two children have NF1, I very quickly got involved with the charity and initially volunteered as a Nurse advisor as part of the medical board and later after leaving my nursing role in the NHS to be a full time carer for my children began working as an educational advocate for the charity. I feel that I have a lot to offer to this discussion in a number of capacities .. · As a person with NF1 who has one diagnosed plexiform tumour for which I have had 5 invasive surgeries and multiple investigations with a possible second plexiform tumour that I am currently undergoing investigations for, I feel that I can discuss my personal experiences of the impacts of surgery on a plexiform tumour as a child/young person and as an adult and also the impact it has had on my life as a whole from the pain/discomfort and bullying/judgement from others to the impact it has on bodily function in my case breathing. · As a parent of two children with NF, one with three diagnosed plexiform neurofibromas, an optic pathway glioma and a pilocytic astrocytoma and the other who has not had full body scans so it is unknown whether they have a plexiform or not, I can talk about the impact it has on my children and on me as a parent including the fight to get scans to get a diagnosis and how hard it can be to get medics to listen and take you seriously and then the fight for treatment and the lack of treatment

	options available – for example my son is awaiting assessment by a plastic surgeon to operate on one of his tumours and the only other option offered to him is to watch and wait. · My daughter who has another condition(lymphatic malformation) which is now in some cases treated with MEK so I know families who have used MEK for this condition and had good results so have knowledge of its other uses/other trails that are currently being undertaken. · From my time as a Paediatric nurse 15 years I have gained experience within the NHS including work in a research team, PICU, NICU and complex care. I feel I can add to the medical discussion about treatment options/management of patients/medical and nursing care of patients as well as an in-site into the medical implications of NF1. · Most importantly I am advocating for member of CTT and the wider NF community, I speak to a number of families on a daily basis who are affected by NF offering advice and support, as a charity we have gathered information from our members about MEK from those who have been placed on the trial, those who have been told they may be eligible after the trail and those who have not been offered MEK or have not heard about it. What is very clear is that the treatment options currently are very limited and there seems to be little understanding of the pain or the psychological impact of plexiform tumours and NF in general. We as a charity support many families/children/young people who we will be looking to fully represent in these discussions. · As an Educational Advocate I am hearing more and more about not only the significant impact that NF has on education but also the impact of optic pathway glioma and plexiform neurofibromas. The loss of education and lack of educational provision for these children is having a very significant impact which could be improved with the development of new treatments/technologies. I feel that as a patient representative I can offer the unique insight not only of a patient with a plexiform tumour but also a mother of a child with multiple plexiform neurofibromas, a pilocytic astrocytoma and an optic pathway glioma , my insight from a medical standpoint/background and the experiences I have of supporting children and young people with NF as a representative of the leading UK NF1 charity that

	solely supports children and young people (and their families) affected by NF1 first as a nurse advisor and now as an educational advocate.
Topic specific questions	
18. Please list all the healthcare resources/medical appointments that you or the child you care for use/attend.	Paediatrician, Neuro-oncologist, ENT consultant, NF specialist nurse, Genetics, NF complex centre, SALT, OT, Physio, Educational psychologist, CAMHS, neurologist, dietician, community paediatrician-neurodevelopmental specialist team, Disability social worker, SEN team at local authority
Key messages	
19. In up to 5 bullet points, please summarise the key messages of your statement:pls see CTT response also ● Currently there is a lack of treatment options for plexiform tumours and gliomas- there is a need for new technologies . ● It is a postcode lottery - who you see, what treatments you get, ● poor knowledge of NF among medics some of who are the main point of contact for children and families ● Lack of pain clinics/ treatments for pain, some medics don't acknowledge pain in NF. ● surgery is not a viable long term option for the majority of patients, multiple surgeries is not acceptable when the end result is negligible - it is unfair to expect people to continue to undergo surgeries that impact on their physical mental emotional social well being and impact their ability to go to school/work etc	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Vanessa Martin**
2. Are you (please tick all that apply):	☐ a patient with the condition? **x**☐ a carer of a patient with the condition? x☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Childhood Tumour Trust
4. Did your nominating organisation submit a submission?	**x**☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised x☐ I have other relevant personal experience. Please specify what other experience: x☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	My daughter was unofficially diagnosed at age 3 but could have been diagnosed a lot earlier we then had to wait over a year for the results of blood test. There was little information around and what was found on the internet was scary. None of the health care professionals looking after my daughter knew much about it and I had to do my own investigations. This had a huge impact on my family as I was told I was over reacting and that my daughter was fine. I felt very isolated and alone with nobody to talk to. I felt I was the only person in the world who had heard of NF1 I was basically sent home from the hospital with my daughter in one hand and a diagnosis in the other and left

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	As it is such an unpredictable condition its very easy to get scared by every new symptom and hard to tell what is to do with NF and what isn't . This is not helped when you go to the GP and they say see your specialist – particularly if you don't have one and often if you ask the specialist they say see your GP.- There are 2 specialist centres in the UK for Complex NF1, those seen under these on the whole get good care but for the other 15,000 plus in England it is hit and miss. School is particularly hard for many of those affected by nf, not only from a learning point of view but feeling left out and not fitting in. This has a huge impact as siblings often get invited to parties and the child with NF1 is not. Some siblings get jealous of the amount of time usually one parent spends with the affected child due to hospital admissions and appointments and this can lead to issues, splitting up siblings and their parents. Work is hard, the feeling every time the phone rings whilst at work dreading that it is the school asking for your child to be collected due to ill health. This on top of having to take days off for hospital/doctor appointments or hospital stays. You need to have very understanding bosses or not work at all. If a child has a physical disability this has an impact on days out. – if they can't walk far a trip to the zoo becomes the equivalent of climbing Mount Everest and again the family can be split up, some staying with affected child and the others going to see more of the attraction.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Treatment and care can be poor and even something as simple as taking Vitamin D is not generally known about. Sometimes NF1 is over treated and other times undertreated. The treatment for the more complex symptoms like plexiforms is limited. My daughter had no quality of life with her large plexiform and was told that it was inoperable and there was nothing they could do. After fighting with so many a plastic surgeon agreed to debulk her tumour – this gave her her life back. Instead of sitting on the sofa doped up on morphine unable to do anything, she could carry on with her education and do things young people should be doing. Also something as simple as being able to wear shorts or trousers meant the world, previous to this she had to live in jogging bottoms. Pain is debilitating and whilst a tumour may not always be life threatening pain can definitely mean life limiting. My daughter would have accepted quality of life over quantity of life. She is now at university working weekends and able to participate in society – and enjoy it. Without having a national pathway of care for those not seen in the Complex centres it is hit and miss and pot luck to what care and treatment they get. If medics are unaware of what is deemed complex they may miss important life threatening signs and not know when or where to signpost for more specialist help. Diagnosis remains poor – and the amount of time waiting for a diagnosis is too long, parents do not know whether to read up on the condition, tell their child or family about it. They are in limbo – often having to chase for a definite diagnosis. They are pushed from pillar to post.

	Without diagnosis it doesn't matter how good treatment or care is, if someone does not know they have the condition. There is an increased risk of breast cancer in those with nf1 (five fold between the ages of 30 -50) this is not known about. Prognosis is good if picked up in time, but without a system in place – it is left to charities to try to let their members know to be vigil and self check often at an earlier age. T
11. Is there an unmet need for patients with this condition?	Totally. It shouldn't be pot luck about where you live or who you see. Everyone with NF1 should expect the same standard of care however it affects them.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and	I assume when you say the treatment you are referring to the MEK? The first advantage is that this offers a treatment that is the first for those with plexiforms. It offers an alternative to surgery, which has its own issues – plexiforms are likely to grow back after surgery, possibly with more chance of malignancy, many surgeons do not like to remove of debulk plexiforms due to blood loss and recovery can be long.

emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	If the MEK can halt growth and reduce pain it will make a huge difference to the lives of those affected. If the MEK had been available for my daughter we may have saved so much time trying to find a surgeon who would operate. She may not have missed so much school and not felt such an outsider or struggle to catch up on missed lessons. She would have been able to join in with more of the sports that she loved to do without having to stop or not even start due to the pain. . She could have worn clothes other than jogging bottoms and gone shopping to buy nice things. She could have worn shorts in the summer and skirts and not felt so self conscious. The impact on her mental health would have been huge. Family days out wouldn't have had to be cut short and possibly the use of a wheelchair would have been avoided, something no 16 year olds wants.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology?	The unknown – what happens when you stop taking it. Any side effects Regular hospital visits at the start - cost of visits and time away from work.

Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	. Some of the side effects are challenging Sickness, bad skin problems, raised intercranial pressure and weight gain, exhaustion. However for many this is short term and the benefits outweigh the negatives. It can be seen as a miracle cure and if it doesn't work on those for which there is no choice and they care taken off it or not started on it, it can have a huge impact on mental health. The lack of pain helps the family to do more things together, but the visits to the hospital can be draining and mean its harder for the family to go on holiday, but the Selumetinib may also mean less visits than when not taking the Selumetinib .
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Some young children may be best put on the Selumetinib to keep the tumour from growing and invasive surgery could be delayed until they are older .

Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**We feel that those with darker skin are under represented within our patient group. We don't know if this means that those with darker skin are not diagnosed as much. On darker skin café au lait (milky coffee) would be darker and sometimes we think that the term café au lait doesn't represent those with darker skin and could be misleading – We think that any multiple skin marks whatever colour should be investigated so that more people can be diagnosed at an earlier age with NF1, rather than wait sometimes until they find they have a plexiform that is cancerous.** As NF1 can be inherited and sometimes the parent has learning difficulties associated with NF1, they cannot advocate for their child as well as others possibly could. They may be struggling with their own issues and also have more than one child with NF1. For parents who have no issues and one child with NF1 it is hard enough.
Other issues	
17. Are there any other issues that you would like the committee to consider?	Will it just be the leads at the NF complex centres who will be able to authorise the Selumetinib or will it be any physician who deems it suitable? - who will decide who is eligible? Some children who could be may eligible may not be under the Complex Centres or even known to them.
Topic specific questions	
18. Please list all the healthcare resources/medical appointments that you or the child you care for use/attend.	Health visitors, Gp's, Orthopaedics, Plastics, speech & language, occupational therapists, pain management, ophthalmologist, physiotherapist, neurologist, gastroenterologists, dermatologists, maxi facial, vascular surgeon, paediatrician, in fact every discipline can cover NF1. I don't refer to any resources as such, as it is very hard to find. . Being a chair of an organisation for those affected by NF1 I attend conferences and read as much as I can to keep updated and use this knowledge to look after my daughter.

Key messages
19. In up to 5 bullet points, please summarise the key messages of your statement: • Better diagnosis amongst early year medics to recognise café au lait marks – and a clear pathway of care from point of diagnosis • Better care for those not seen under the complex centres and a clear pathway to refer when needed to the Complex Centres • Better acknowledgement of pain and treatment for it – holistic treatment needed – one point of contact not spread out over disciplines and hospitals • Links to help families – patient organisations, financial support, benefits etc • More financial support from the government into research, care and treatment

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr. Grace Vassallo**
2. Name of organisation	**Manchester University Hospitals NHS Foundation trust**

3. Job title or position	**Consultant Paediatric Neurologist RMCH Clinical lead for the HSS Complex NF1 service in Genomic Centre for Medicine Manchester.**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	NF1 is a common genetic disease. By and large the majority of individuals affected are well. A small minority have devastating complications. The NHS HSS for complex NF1 was set up by NHS England to improve the health of this small minority of complex NF1 patients. One of the most important and devastating complications of this disease is a plexiform neurofibroma. Up to 50% of individuals with NF1 have one but in very few these plexiforms are so serious that they are classed as " Symptomatic inoperable plexiform neurofibromas". Described best by our nurse lead for the service in Manchester Mrs. Judith Eelloo as the " roots of a massive tree" these plexiforms which are a tangled mass of tumours from nerves, blood vessels and fibrous tissue grow, infiltrate, compress and erode structures in their vicinity. The growth of these rare but devastating tumours progresses quickly in childhood and then usually stabilize in adulthood but by than the life of the individual and that of their family is affected for ever. Spines are bent and need repeated spinal surgery, spinal cords are compressed with loss of function, airways are compressed and tracheostomies needs, pain becomes constant-unresponsive to medication and becomes chronic and embedded. Bodies and limbs are disfigured.Education is lost and the child`s life evolves into an adult with chronic ill health, chronic pain very often with no employment, reliant on family for help and with mental health problems.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The primary end point of the literature and the studies being considered is a sustained reduction of at least 20% in a fair percentage of children (70%). Later studies discussed other outcomes which in my opinion are much more important and are what really ultimately changes the future for these children. Outcomes such as pain reduction/quality of life and improved motor function. The effect on size reduction-this is of course excellent when it happens as it lessens disfigurement and in a very small minority can be life preserving eg when the plexiform surrounds the heart and major blood vessels.However what is really important is that the greater majority of the plexiforms treated do not continue to grow. (some do but a very small proportion and in those children one would not usually continue treatment). The plexiform become softer and their progressive infiltration, distention of tissues and destruction is halted-in a significant proportion of treated children this is absolutely life changing with dramatic results.

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are always unmet needs for children and health professionals in any condition however it is clear that in working together we always strive to improve outcomes. NHS England has started this process in 2009 by establishing the HSS NF1 service for complex NF1. The aim was to reduce mortality from MPNST (when a plexiform turns from benign to malignant) and to improve morbidity by centralizing care. There has never been medication that has made any difference to plexiforms before. The only treatment was repeated mutilating surgery if possible (sometimes with amputations of limbs) with at times significant loss of function and severe disability to preserve life. There is now an opportunity to make a difference to a small group of children at an age where they would benefit at an age when the rate of the growth of the symptomatic inoperable plexiform is at its height.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Two centralized HSS NHS funded complex services in Manchester and London are the two quaternary centres in the UK that have over the past 11 years collected an expert MDT group of consultants with an accumulated experience of looking after these patients. Up till now treatment was aimed at minimizing morbidity from surgery that was unlikely to achieve any positive outcome. This conservative management is important but hard for families for whom no alternative treatments was possible. The options were to tolerate the situation, to provide surgery if there was a threat to life with the acceptance of mutilation/morbidity and at times mortality (they are very vascular and patient may bleed to death despite expert care) or to provide short term surgery with repeated surgeries over the years for a plexiform that simply grows again. This drug offers the chance to change this-there is no doubt that it is not a miracle cure but it has its role and the complex NF1 services will have the skills to select the correct group of children that should be offered the treatment. The two services are already doing this and have been doing for the last few years. Two groups of children have been offered MEK inhibitors. A group at GOSH who are undergoing a TRIAL (These are children from all over England) and a group of children who have been offered these drugs on compassionate grounds (threat to life) All these cases are discussed at three monthly national MEK inhibitor MDTs and only the appropriate children who are felt to be eligible are offered the medication. These MEK inhibitor MDTs are all consultant led with all the relevant Consultant Specialists present. (Paediatric Neurologists/ Paediatric Neurooncologists/ Plastic surgeons / nurses etc)

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are guidelines that have been developed at GOSH which have been shared with the Manchester team. They have been developed by Prof D Hargreaves who is an international expert of the use of MEK inhibitors in general (these drugs are used for other tumors)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are always differences of opinions between people-it would be unhealthy if there were not! However professionals always ultimately retain their focus on what is best for their patients and represent their interest. The pathway is well established and is already being used. Children with symptomatic inoperable plexiforms are referred to the two national centres where they are evaluation for eligibility. The referrals often come from oncologists from big tertiary hospitals but sometimes from paediatricians. Manchester has already established hub and spoke links with Newcastle and Leeds and is working to build further hubs. This pathway is nationally agreed in principle between the two centres but its ultimate establishment will depend on the outcome of this NICE evaluation. (As in if the drug is approved)
• What impact would the technology have on the current pathway of care?	NHS England are aware of this drug and has already initiated processes for structuring of funding around it. In terms of impact on the patient pathway-they will have more investigations and more evaluations but their ultimate outcome will be improved in the great majority. They will be constantly evaluated and if the drug is not helping than it will be stopped after appropriate MDT discussion. In terms on the impact on the service-this will be significant. The children will need regular blood tests/eye checks/echocardiograms/scans/ input by the oncologists/hours for new specialist NF1 MEK inhibitors nurses, dermatologist. All the infrastructure is there, all the human resources are there we will simply need more hours of time to cater for this new branch of the service that actually involved treating without repeated surgery.
11. Will the technology be used (or is it already used) in	Yes Manchester already has around 10 children on MEK inhibitors on compassionate grounds. Some are shared with our satellite hubs. GOSH have more (some of the Manchester patients) as they are running the INSPECT trial. In our group of compassionate patients we have had some outstanding life changing results that have been presented to NHS England CQUINN October 2021.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There has never been a medication that can help with symptomatic plexiform neurofibromas. The previous pathway of care has been explained above.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Quaternary centres only in terms of selection of patients who will be presented in the national MEK inhibitor MDTs- Manchester and London to lead patient selection but hubs across England with paediatric oncology centres who are interested. Paediatric Oncologists already use MEK inhibitors for other tumours and have experience of it. Families appreciate being treated by their teams closer to home and the centres appreciate working collaboratively with us. This is already in place in the North and working well.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Experience from our collection of patients on compassionate use has taught us that we need more time of the following who are already part of the team. Paediatric Oncologists Paediatric radiologists Paediatric Neurologists Paediatric plastics Paediatric Opthalmologist We need new resources that are available within the Trust but their time needs to be equated in planning Physios and OT/Paediatric NF1 MEK Inhibitor nurse/Dermatologist/ pain specialist/podiatrist Resources for increased MR scans Increased blood tests Increased Echos

	Resources for the medication itself and dealing with the side effects Skin and nail infections mostly (creams and antibiotics and podiatrist and washes)
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Undoubtedly
• Do you expect the technology to increase length of life more than current care?	Not massively (perhaps single individuals) as these children rarely die from their benign plexiform though a very few do. I can honestly say that out of our Manchester cohort two of our children have had their lives probably saved by this drug and in one definitely the quality of life is also massively improved. There is absolutely no data at all for us to understand what impact this drug will have in potentially preventing MPNST in the future thought theoretically it may do so. (One could hypothesise that it could)
• Do you expect the technology to increase health-related quality of life more than current care?	Undoubtedly for the correctly selected patients. It is also important for us to remember that these patients are constantly evaluated and we would not recommend ongoing treatment if it is simply not providing benefit.
13. Are there any groups of people for whom the technology would be more or	

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	All these questions have been answered above. This is standard oral treatment with a class of drugs that is already being used in the paediatric oncology group of patients. Additional time of clinicians/nurses/AHPs and additional blood and MR scans are needed but they are all available and ready to be of service.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are rules as adopted by the SPRINT trial that would be discussed with the families but in our experience the family who it is not helping will ask themselves for the drug to be stopped as they perceive no benefit and they do not like the added intrusions or the skin and nail side effects if they have no gain.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	I have no doubt that it will. It will improve the way current needs are met because the only way we can meet SOME needs but not all is surgery and in this group of patients surgery is simply to dangerous to offer-it may mutilate/lead to loss of life or function. The criteria for this medication is symptomatic inoperable plexiform and so by definition surgery is not offered unless some surgery can be done to prolong life- eg tracheostomy for neck plexiforms.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes as explained in my answer above
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common side effects are skin rashes and nail bed infections. The management of these is very much assisted by a dermatologist and a podiatrist plus the protocol of skin care that is available and which we continue to work and improve on constantly.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	In the greater majority yes. The one big problem we all face is the concept of measuring plexiform volume. The trail had a group of neuroradiologists that painstakingly measured all the volumes themselves for hours on end. This would not be possible in real day to day practice but we are working with AI developments to

	assist us. In the UK our radiologists feel that they can select section of the most relevant parts of the plexifroms and use those to measure volume response. Increasingly however we are using the volumes in tandem with other much more measurable outcomes eg Pain, texture, leg length discrepancy, airway patency etc
• If not, how could the results be extrapolated to the UK setting?	As explained above in terms of " volumetrics"
• What, in your view, are the most important outcomes, and were they measured in the trials?	Pain -yes Size/volume- yes Treat to function (eg spinal cord/airway) Disfigurement- Yes but challenging to evaluate
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes- eg number of surgeries needed to manage leg length discrepancy Spinal cord compression progression prevention (clinical and radiological) Reversal of tracheostomies

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	More trails are underway and there will be added information from them however what we are seeing in day to day practice does not differ much from published data in trials.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	In ongoing Trials
21. How do data on real-world experience compare with the trial data?	Very similar
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

22b. Consider whether these issues are different from issues with current care and why.	
Topic specific questions	
23. Are age, plexiform neurofibroma (PN) volume and PN location expected to be treatment effect modifiers?”	Age is by far the main one however location is also very important particularly in the plexiforms that abut the spinal cord and the major airways as in both these locations the impact of an increase in size in the order of a few mm is catastrophic.
24. Do patients receiving current treatment all have progressive disease or can some patients stablise for a period, before their disease progresses?	The trials are clear the a few progressed, many regressed and some stabilized. This is similar to our experience. One child now has progression in one part of his plexiform. Some have regressed and the rest have stabilized.
25. After 18 years of age does the tumour size plateau? Would a patient then	That is what is stated in the literature. No one cannot say that- we have many adult patients in whom their disease progresses slowly but not in the explosive way that we sometimes see in paediatricis.

experience no further disease progression?	
26a. To better understand what costs are involved in treating patients, what are the current healthcare resources used/ medical appointments attended by patients, for both a child, and as an adult?	Complex NF1 patients are usually seen on a yearly basis as a minimum with yearly scans. Patients with symptomatic inoperable plexiform are seen much more frequently because of pain, complications, further opinions from surgeons etc. The patient who will be on MEK inhibitors if this drug is approved will initially need many visits for evaluations, tests etc but as things stability all this settles to around three monthly MDT evaluations. (The oncologists will have more details on this)
26b. On average how many MRI scans would a patient receiving selumetinib have per year compared to best supportive care?	The recommendation at the start was 3 monthly but now has moved to 6 monthly. Usually we do yearly scans in patient who are undergoing supportive care with significant plexiforms.
Key messages	

27. In up to 5 bullet points, please summarise the key messages of your statement.

- MEK inhibitors are well tolerated and available in oral form.
- Their side effects are manageable if they confer benefit and patients who have benefitted from them will be very accepting of the investigations and side effects.
- They can be lifesaving in single figure patients
- They can be life changing in a correctly selected group of patients
- They are the first real opportunity we have ever had to treat this very compromised select group of patients
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over (ID1590)

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Any de-personalised data are highlighted in pink throughout the report.

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Pim Wetzelaer, Hannah Penton, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Susan O'Meara and Charlotte Ahmadu acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance on the health economics part of the project. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

6MWT	Six-minute walk test
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AHI	Apnoea hypopnoea index
AiC	Academic in confidence
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASPHO	American Society of Pediatric Hematology/Oncology
AUC	Area-under-the-curve
AZ	AstraZeneca
BIC	Bayesian information criterion
BID	Twice daily
BNF	British National Formulary
BOR	Best objective response
BSA	Body surface area
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Commercial in confidence
CMT	Clinically meaningful threshold
CPAP	Continuous positive airway pressure
cPR	Confirmed partial response
CR	Complete response
CRD	Centre for Reviews and Disseminations
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DALY	Disability-adjusted life-year
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DMD	Duchenne Muscular Dystrophy
DP	Decision problem
DVQ	Dysfunctional voiding questionnaire
ECG	Electrocardiogram
ECHO	Echocardiogram
EQ-5D-5L	European Quality of Life-5 dimensions-5 levels
ERG	Evidence Review Group
ESHPM	Erasmus School of Health Policy & Management
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FEV0.75	Forced expiratory volume after 0.75 seconds
FEV1	Forced expiratory volume after 1 second
GIC	Global impression of change
HR	Hazard ratio
HRQoL	Health-related quality of life

HST	Highly specialised technologies
HSUV	Health-state utility value
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
iMTA	Institute for Medical Technology Assessment
INAHTA	International Network of Agencies for Health Technology Assessment
Inc.	Incremental
IPTW	Inverse probability of treatment weighting
ISPNO	International Symposium on Pediatric Neuro-Oncology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
JGNC	Joint Global Neurofibromatosis Conference
KSR	Kleijnen Systematic Reviews
LYG	Life years gained
MA	Meta-analysis
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject heading
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed-effect model repeated measures
MMT	Manual muscle testing
MPNST	Malignant peripheral nerve sheath tumour
MRI	Magnetic resonance imaging
N	Number of participants included in analysis
N/A	Not applicable
NCI	National Cancer Institute
NCPE	National Centre for Pharmacoeconomics
NF	Neurofibromatosis
NF1	Type 1 neurofibromatosis
NH	National History Study
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NRS-11	Numerical rating scale 11
ONS	Office for National Statistics
ORR	Objective response rate
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PASLU	Patient access scheme liaison unit
PBMC	Peripheral blood mononuclear cells
PEDE	Paediatric Economic Database Evaluation
PedsQL	Pediatric Quality of Life Inventory
PEG	Pegylated
PFS	Progression-free survival
PFT	Pulmonary function test
PII	Pain interference index
PN	Plexiform neurofibroma
PR	Partial response
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analyses

PSS	Personal Social Services
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation in Solid Tumours
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SAE	Serious adverse event
SAP	Safety analysis plan
SAS	Safety analysis set
ScHARRHUD	University of Sheffield Health Utilities Database
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMR	Standardised mortality ratio
SOC	System organ class
Std. Diff.	Absolute standardised difference
TA	Technology appraisal
TACQOL	Netherlands Organization for Applied Scientific Research Academic Medical Centre (TNO AZL) Children's Quality of Life
TE	Treatment effect
TTD	Time to discontinuation
TTO	Time trade off
TTP	Time to progression
Tx	Treatment
UK	United Kingdom
US	United States (of America)
USA	United States of America

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1. SUMMARY

1.1 Background

Type 1 neurofibromatosis (NF1) is a rare, complex, and incurable disease in which symptoms manifest in early childhood and continue into adulthood. Approximately one quarter of patients with NF1 go on to develop non-malignant peripheral nerve sheath tumours known as plexiform neurofibroma (PN).

Symptoms of NF1 manifest across multiple organ systems, and can affect the nervous system, skin, bones, and eyes. PNs can occur anywhere in the body and may cause substantial morbidities due to their invasiveness and size, e.g. causing pain, impact on vision, motor skills, breathing, bladder and bowel function, or result in disfigurement.

Currently, surgery is the only available treatment to reduce or remove PN tumours. However, as PN are large and invasive, approximately half of all patients with NF1 PN are considered inoperable (defined as PN which cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity).

The company submission (CS) estimated the total eligible to be 37 patients within the United Kingdom (UK) while the Evidence Review Group (ERG) notes that an estimate almost twice as high (70) could be considered reasonable based on the evidence presented in the CS, see Section 2.2.2 for details. The ERG explored this in a budget impact analysis, reported in Section 7.2.

It should be noted that the company did not support all information with relevant references, e.g. some statements in Section 2 of the CS, although plausible, were not supported by references.

Selumetinib has received orphan drug designation and conditional marketing authorisation from the European Medicines Agency (EMA) for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above. Selumetinib was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2021.

1.2 Critique of the decision problem in the company's submission

Overall, the decision problem (DP) addressed by the company is in line with National Institute for Health and Care Excellence (NICE) scope.

- Population: Children aged 3 years and over with symptomatic and inoperable PN associated with NF1.
- Intervention: Selumetinib 25 mg/m^2 body surface area twice daily.
- Comparators: Established clinical management without selumetinib. Note: The CS noted that this includes pain management (prescription and over-the-counter painkillers).
- Outcomes: In addition to 10 outcomes specified in the NICE scope (complete response (CR) and partial response (PR) rate, growth rate of PN, disfigurement, physical functioning, visual function, airway functioning, bowel and bladder continence, pain, adverse effects (AEs) of treatment, and health-related quality of life (HRQoL) of children), the company added four outcomes, namely duration of response, progression-free survival (PFS), time to progression (TTP), and global impression of change (GIC) (see Section 3.3.4 for details).
- Cost to the National Health Service (NHS) and Personal Social Services (PSS): Cost effectiveness analysis (CEA) results presented in the form of incremental costs per quality-adjusted life years (QALYs) over a lifetime time horizon, with the impact of treatment on the HRQoL of patients and caregivers included in the analysis. Costs calculated according to the NHS and PSS perspective. Costs and QALYs discounted at 3.5%.

1.3 Summary of clinical effectiveness evidence submitted by the company

Clinical efficacy results were presented from the SPRINT Phase II Stratum I trial (a single-arm study recruiting 50 patients from four centres in the United States of America (USA)), and comparisons were made with the National Cancer Institute (NCI) Natural History study (93 age-matched individuals) and the placebo arm of the tipifarnib study (29 participants). These are reported in Section 4.2.4 and summarised below:

- Results suggested that more participants receiving selumetinib in SPRINT Phase II Stratum I experienced a reduction in PN volume of at least 20% when compared with usual care in the NCI National History study (68% vs. 0%).
- 45 patients (90%) treated with selumetinib in SPRINT Phase II Stratum I had a best objective response (BOR) of reduction in PN volume from baseline, and 37 patients (74%) experienced at least 20% reduction in PN volume at BOR.
- The median time to initial response in SPRINT Phase II Stratum I was 8 cycles (range 4 to 20), and the median time to best response was 16 cycles (range 4 to 36).
- None of the participants receiving selumetinib in SPRINT Phase II Stratum I displayed a PN growth rate of 20% or more per year (range -27.0% to 19.8% per year), compared with 43% of patients in the age-matched cohort of the NCI Natural History study.
- The median PFS was not reached in SPRINT Phase II Stratum I at data cut-off (DCO) 29 March 2019. At 3 years, 84% of patients in SPRINT Phase II Stratum I remained progression-free compared with 15% in the NCI Natural History age-matched cohort.

With respect to safety and AEs, at a DCO of 29 March 2019 for the SPRINT Phase II Stratum I study, [redacted] of patients experienced AEs, [redacted] of patients experienced Grade ≥3 AEs, and [redacted]. Results for two additional studies, reporting on 28 participants, are in line with these findings, details can be found in Section 4.2.4.2.

As there were no head-to-head trials comparing selumetinib to established clinical management, naïve comparisons were conducted between SPRINT Phase II Stratum I, an age-matched cohort from the NCI National History study, and the placebo arm of the tipifarnib study. In addition, to explore the potential impacts of adjusting for baseline covariates across the study population, the company undertook a propensity score analysis. The results showed a statistically significant advantage of selumetinib compared to 65 participants of the Natural History age-matched cohort, e.g. [redacted]. Results were highly consistent across all four additional analyses and demonstrated a high degree of robustness to the choice of method used for comparison. However, these results were based only on PFS, where progression was defined as ≥20% increase in PN volume, which was not listed in the NICE final scope. Therefore, on request by the ERG the company supplied propensity score analyses of PN growth rate, which also showed a clear advantage to selumetinib regardless of choice of method used for the comparison.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The detailed ERG's summary and critique of the clinical effectiveness evidence submitted by the company can be found in Section 4 of this report. The key issues highlighted in the ERG's critique are summarised in Tables 1.1 to 1.3.

The CS and response to the request for clarification provided sufficient details for the ERG to appraise the searches and conclude that they had been generally well conducted. The methods of data extraction

and quality assessment were not in line with best practice, e.g. the Cochrane Handbook states that at least two people should work independently on the risk of bias assessment.

The ERG assessed the relevance of all eight studies identified by the systematic literature review (SLR) and identified two studies in addition to the main source of data (SPRINT Phase II Stratum I) which had been judged by the company to be the only study identified in the SLR as being relevant to the DP. Adverse events data from these two studies were included in Sections 4.2.4.2.2 and 4.2.4.2.3, respectively.

The generalisability of SPRINT Phase II Stratum I to the UK population can be called into question as it was conducted in the USA, and no UK patients were included. However, the company justified this by stating that, *"based on an assessment of baseline characteristics, patients from the SPRINT Phase II clinical trial are broadly representative of the UK paediatric NF1 PN patient population, despite being recruited from US sites, which has been confirmed by clinical experts in the UK".*

Table 1.1: Key issue 1: Robustness of identified clinical effectiveness data

Report Section	**4.2.1**
Description of issue and why the ERG has identified it as important	Lack of comparative studies: all trials included for efficacy and safety data, i.e. SPRINT Phase II Stratum I, Baldo et al. 2020, Espirito Santo et al. 2020, are single arm trials.
What alternative approach has the ERG suggested?	Studies directly comparing selumetinib with relevant comparators would decrease uncertainty.
What is the expected effect on the cost effectiveness estimates?	The uncertainty is increased.
What additional evidence or analyses might help to resolve this key issue?	Studies directly comparing selumetinib with relevant comparators would decrease uncertainty.
ERG = Evidence Review Group	

Table 1.2: Key issue 2: Proportion of paediatric NF1 patients with PN might be higher than stated

Report Section	**2.2.2 and 7.2**
Description of issue and why the ERG has identified it as important	The total eligible patient population might be roughly twice as big as stated in the CS. This may result in a higher proportion of patients with NF1 and PN being eligible/considered for selumetinib treatment.
What alternative approach has the ERG suggested?	Include as scenario in budget impact analysis.
What is the expected effect on the cost effectiveness estimates?	As detailed in Section 7.2, this has a considerable impact on the budget impact analysis.
What additional evidence or analyses might help to resolve this key issue?	Further data to get a more robust estimate of the eligible target patient population relevant for this submission.
CS = company submission; ERG = Evidence Review Group; NF1 = type 1 neurofibroma; PN = plexiform neurofibroma	

Table 1.3: Key issue 3: Propensity score matching being based on progression

Report Section	4.2.4.4 and 5.3.3
Description of issue and why the ERG has identified it as important	Propensity score matching (albeit a robust method) was based on an outcome of limited clinical value not defined in the final NICE scope, namely progression-free survival.
What alternative approach has the ERG suggested?	On request by the ERG the company supplied propensity score analyses of PN growth rate, which also showed a clear advantage to selumetinib regardless of choice of method used for the comparison.In addition the company demonstrated that such an analysis of ORR was nugatory given ORR of 0% in the Natural History study.
What is the expected effect on the cost effectiveness estimates?	The results were not used to inform the economic model. However, in principle, these could have been used in the economic model.
What additional evidence or analyses might help to resolve this key issue?	Implementation of PN growth rate propensity analysis in a patient-level model.
ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence; PN = plexiform neurofibroma	

1.5 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The searches reported for the SLR were clearly structured and documented. Searches were carried out on a broad range of resources, including supplementary searches of conference proceedings and other relevant resources such as a trials database, company records and the checking of references lists to identify additional studies not retrieved by the main searches.

The company presented a de-novo area-under-the-curve model to assess the cost effectiveness of selumetinib in NF1 PN. The model consists of three health states, which are defined based on the natural history of disease progression as either stable/non-progressive disease, progressive disease or dead. The model includes 100 annual cycles, representing thus a lifetime horizon, with the impact of treatment on the HRQoL of patients and caregivers included in the analysis. Costs are calculated according to the NHS and PSS perspective. Both, costs and QALYs were discounted at 3.5%.

Patients in the best supportive care (BSC) arm enter the model at the progressive disease health state and are assumed to receive pain medications and treatment for symptom relief only. Patients in the selumetinib arm also enter the model at the progressive disease health state but are assumed to experience disease stabilisation within the first year of treatment and remain in the progression-free state until disease progression. Given that 16% of patients experienced progression during the 3-year SPRINT follow-up, the observed data were used to estimate an annual progression rate of 5.6% per year. Once patients reach the age of 18 years, their tumour size is assumed to stabilise and therefore no progression events are assumed to occur after the age of 18 years.

Treatment discontinuation was modelled based on parametric extrapolations of patient-level data on time to discontinuation (TTD) from SPRINT Phase II Stratum I. Several parametric distributions were explored for the extrapolations of TTD. Selection of the most appropriate distribution was informed by goodness-of-fit statistics, visual inspection of the extrapolated curves and clinical expert opinion. All curves were judged to be similar based on goodness of fit values and visual inspection of the curves

against the trial data. Final selection was guided by clinical plausibility. From this, the extrapolation using a Weibull distribution was chosen as the most appropriate based on the expectation that discontinuation rates will be highest when patients reach adulthood. Given the paediatric license for selumetinib, maximum duration of treatment was assumed until patients reach the age of 18 years.

Mortality rates were informed by UK life tables with the addition of a standardised mortality ratio (SMR) to account for a reduced life expectancy associated with NF1-related comorbidities (the company indicated that a PN-specific rate was not available from the literature). No benefit of selumetinib on mortality was assumed.

Grade ≥3 AEs that occurred in greater than 5% of patients in SPRINT were included in the model. This included diarrhoea, vomiting, pyrexia (fever), hypoxia, paronychia (infection of the skin around fingernails and toenails) and dermatitis acneiform. Most were of short duration (less than a week), except for paronychia and dermatitis acneiform. Adverse events were assumed to impact the cost calculations in the model only; thus, no impact on HRQoL was assumed.

The company conducted a vignette time trade off (TTO) study to estimate utility values for on-treatment and progressive disease health states for the model. All patients entered in a progressive state with a utility of [redacted]. Upon treatment initiation, patients receiving selumetinib were assumed to experience a linear increase over 1 year to the on-treatment utility value of [redacted], which was applied until progression. The company assumed that upon progression, patient's utility linearly declines from [redacted] to [redacted] over a period of 5 years. From the age of 18 years, as no progression events are assumed to occur, utility is assumed to remain stable. If a patient experiences a progression event prior to 18 years but has not yet reached the progression state utility of [redacted], they keep that mid-way utility for the remainder of their lifetime. Therefore, the treatment benefit observed at 18 years is considered a lifetime benefit of treatment. Age-related decline in utilities is assumed, however there is no impact of discontinuation on utility. Carer disutilities were assumed to be equal to the treatment effect applied to patients ([redacted]). This disutility was applied to 1.4 carers per patient, as the average household size in the UK is 2.4 persons.

Patients in the selumetinib arm accrue treatment costs (while on selumetinib treatment), AE costs and magnetic resonance imaging (MRI) costs. Patients in the BSC arm accrue costs of pain medication.

1.6 Summary of the ERG's critique of the value for money evidence submitted

The ERG's summary and detailed critique of the value for money evidence submitted by the company can be found in Section 5 of this report. The key issues in the value for money evidence are summarised in Tables 1.4 to 1.8.

Table 1.4: Key issue 4: It is unclear whether the structure of the economic model is appropriate to model the natural progression of the disease

Report Section	**5.3.2**
Description of issue and why the ERG has identified it as important	Throughout the CS, the heterogeneity of NF1 and PN is emphasised. The evidence provided also suggests that PN growth rate strongly varies with age, that age is expected to be a treatment effect modifier and that PN volume and number of PN-related morbidities are expected to be treatment effect modifiers. All these associations are not captured by the current model.
What alternative approach has the ERG suggested?	A patient-level model might be more appropriate to model the natural progression of the disease.

Report Section	5.3.2
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The committee should be aware of the limitation of the current modelling approach and decide whether the current economic model is fit for purpose. A patient-level model might overcome the issues described above.
CS = company submission; ERG = Evidence Review Group; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibroma	

Table 1.5: Key issue 5: PFS modelling seems too simplistic

Report Section	5.3.3.3
Description of issue and why the ERG has identified it as important	The PFS approach in the selumetinib arm seems too simplistic: only a constant annual probability of progression was used. Despite the evidence presented by the company suggesting otherwise, there is no PFS with BSC: patients are assumed to remain in the progressed disease health state.
What alternative approach has the ERG suggested?	Full parametric modelling in selumetinib arm. Include PFS in BSC and then full parametric modelling in BSC arm.
What is the expected effect on the cost effectiveness estimates?	Unknown but including PFS in BSC is expected to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Survival analyses on selumetinib and BSC data. Implement the results in the economic model.
BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; PFS = progression-free survival	

Table 1.6: Key issue 6: The assumption of 5-year waning of utility after progression is unclear

Report Section	5.3.3.7
Description of issue and why the ERG has identified it as important	The company assumed that upon progression, patient's utility linearly declines from [redacted] to [redacted] over a period of 5 years. No justification was provided as to why 5 years was assumed. This assumption is combined with another which assumes that patients' utility remains the same from the age of 18 years as no progression events are assumed to occur beyond this age as tumour size is assumed to plateau. If a patient experiences a progression event prior to 18 years but has not yet reached the progression state utility of [redacted], they keep that mid-way utility for the remainder of their lifetime. Therefore, the treatment benefit observed at 18 years is considered a lifetime benefit of treatment. Stability of utility after 18 years of age, combined with a 5-year post-progression waning can provide a substantial lifetime treatment benefit for which no evidence is presented.
What alternative approach has the ERG suggested?	The ERG considers a linear decline in utility over one-year post-progression to be more appropriate, given that a) this equals the period assumed to observe the full treatment effect at treatment initiation and b) that the vignettes upon which progression free and progressive utility

Report Section	5.3.3.7
	values are based are not based on a certain lump (PN) size, but only on the fact that the lump is growing, and no treatment is being received. This applies from progression.
What is the expected effect on the cost effectiveness estimates?	Replacing the 5-year waning utility period with 1-year increases the company base-case ICER by approximately £9,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	HRQoL data measured directly in patients pre- and post- progression using a generic preference-based measure are required to understand how utility changes over time. However, estimating utility as a function of tumour size might be more suitable for a patient-level model, as recommended in key issue 4.
ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; PN = plexiform neurofibroma; QALY = quality adjusted life year	

Table 1.7: Key issue 7: Uncertainty in utility values and carer disutilities

Report Section	5.3.3.7
Description of issue and why the ERG has identified it as important	The utility values used in the model were estimated using a vignette study in which health states for being progression-free on treatment with selumetinib and progressive off-treatment were developed and valued by members of the UK general population. This means that the utility values were not estimated using patient reported data and they rely solely on the ability of the general population respondents to imagine the health state based on the description provided. Health states revolved around the impact of a "large lump" on various aspects of QoL and it is unclear how accurately participants would be able to conceptualise this. Additionally, health state descriptions were lengthy which could lead to the use of heuristic shortcuts and use of bolding may have focussed participants on the more positive elements of the treated state and the more negative elements of the untreated state encouraging focussing effects. Carer disutilities were assumed to be equal to the relative treatment effect applied to patients (patient treatment effect = [redacted]). This disutility was applied to 1.4 carers per patient, as the average household size in the UK is 2.4 persons. No evidence specific to carers in this population was presented to substantiate either of these assumptions. A recent review of carer disutilities in NICE appraisals showed that the assumed disutility of approximately [redacted] was substantially larger than disutilities applied in other appraisals, including a disutility of 0.11 for caring for a non-ambulatory child with Duchenne Muscular Dystrophy and a disutility of 0.07 for carers of children with activity limitations. The ERG did not consider the assumption that everyone except the patients in an average household UK would be a carer appropriate, as there could well be other children in the household. Given that most appraisals which included a carer disutility had applied it to only one carer, this approach was considered more appropriate given the lack of data.
What alternative approach has the ERG suggested?	HRQoL should be measured directly in patients with stable and progressive disease and carers using a generic preference-based measure.

Report Section	5.3.3.7
What is the expected effect on the cost effectiveness estimates?	The impact of uncertainty in the patient utility values is unknown as no alternative utilities are available to indicate whether the treatment effect estimated is appropriate, over-, or under-estimated. The appropriate carer disutility is also unknown, however reducing it to 0.07 in one carer increases the company base-case ICER by £28,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	HRQoL data measured directly in patients pre- and post- progression and carers using a generic preference-based measure are required to understand how patient utility changes over time and the impact on carers. The company could also map the PedsQL data from the SPRINT trial to provide some validation of the patient utilities obtained from the vignette study. Also, estimating utility as a function of tumour size might be more suitable for a patient-level model, as recommended in key issue 4.
ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NICE = National Institute of Health and Care Excellence; PedsQL = Pediatric Quality of Life Inventory; QALY = quality adjusted life year; QoL = quality of life; UK = United Kingdom	

Table 1.8: Key issue 8: A limited number of cost items is included in the analysis

Report Section	5.3.3.8
Description of issue and why the ERG has identified it as important	The included cost items are limited to drug acquisition costs for selumetinib, the costs of additional MRI scans for patients receiving selumetinib, pain medication costs, and costs for the medication used in the management of treatment-related AEs. Not all relevant costs are included. The company indicated that this was due to the heterogeneity in patient and symptomatic management and that there is no specific data to support a quantitative difference in the symptom management costs other than pain medication costs.
What alternative approach has the ERG suggested?	No alternative approach is suggested by the ERG. Although it would be conceivable to include data from literature sources on health care resource use in relation to patient and symptomatic management in BSC, the ERG knows of no data available to inform health care resource use for patients treated with selumetinib.
What is the expected effect on the cost effectiveness estimates?	The ERG agrees with the company that treatment with selumetinib is likely to reduce patient and symptomatic management costs and that the exclusion of these costs may be a reason to interpret the cost effectiveness results as conservative estimates.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion consulted by the company indicated that the following, additional types of health care resource use are or may be relevant to consider for patients with symptomatic, inoperable NF1 PN: clinical nurse specialist support, educational support, physiotherapy, psychological support, occupational therapy, clinical appointments for the follow-up and monitoring of treatment with selumetinib, and the use of medication for anxiety and depression in adult patients. Other cost items of possible relevance, as indicated by literature, include outpatient visits, emergency room visits, inpatient visits, and chemotherapy. The inclusion of data on all relevant cost items, both for patients treated with selumetinib and with BSC, would provide a more comprehensive picture on costs.

Report Section	5.3.3.8
AE = adverse event; BSC = best supportive care; ERG = Evidence Review Group; MRI = magnetic resonance imaging; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibroma	

1.7 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The proportion of costs outside of the NHS and PSS that may be saved due to treatment with selumetinib, or of the additional benefits other than health, have not been estimated by the company. In the CS there is only some narrative describing potential savings outside of the NHS and PSS.

The CS also states that while the impact of selumetinib on cost and cost savings to UK government bodies has not been explicitly investigated, selumetinib may be expected to bring cost savings to government bodies other than the NHS due to improvements in patients' daily lives (e.g. improved school attendance), reduced patient disability, and improved parent/carer productivity.

The company also indicated that parents and other carers often experience a loss of income due to time spent on caring for the patient. Interviewed UK clinicians indicated that family members, often the parents, spent a substantial time on care, leading to loss of productivity. This may continue into adulthood of patients. However, this time spent on care was not quantified by the company.

Costs may also occur when home adaptations and aids are required and additionally, for adult patients some costs may also occur for vision aids. However, none of these costs were quantified in the CS.

Finally, according to the company, selumetinib represents a step change in the management of NF1 PN as it is the first licensed disease-modifying treatment for NF1 PN. This may lead to increased understanding of the long-term impact of disease-modifying treatment for PN, which might also lead to further innovations in the care of patients with symptomatic, inoperable PN.

1.8 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health-related benefits

The CS includes some narrative about costs outside the NHS and PSS; however, no attempt to quantify these costs has been provided. The company argue that some of these costs may be saved when patients are treated with selumetinib, given that treatment is expected to reduce PN-associated morbidities. However, there is currently no evidence to indicate to what extent reduced morbidity will lead to savings in societal, patient, and carer costs.

1.9 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

Strengths: The ERG believes that the following represent strengths within the CS:

- The DP addressed in the CS aligns with the NICE final scope.
- Searches for clinical effectiveness evidence were well conducted.
- The CEA was performed in line with the NICE final scope. Thus, it is relevant for the DP addressed in this submission.
- The company presented the first CEA for children with NF1 PN. The analysis aligns with the NICE reference case. The model developed reflects to some extent the disease progression and its impact on HRQoL.
- Time on treatment is based on parametric extrapolations of patient-level data from SPRINT Phase II Stratum I that were performed appropriately.

- The company also attempted to address the evidence gaps around utilities by conducting a novel TTO study specifically aimed at eliciting NF1 PN utility values.

Weaknesses: The following are the main weaknesses of the CS, observed by the ERG:

- The clinical effectiveness evidence comes from small single-arm studies.
- The SLR conducted for the clinical effectiveness section does not follow best practice.
- Two additional studies, identified by the company, are relevant to the DP.
- The economic model does not capture the heterogeneity and important aspects of the natural progression of the disease: in particular, PFS precludes the effect of variation in PN growth rate.
- The modelling approach to PFS is simplistic, applying a constant annual probability of progression and only for selumetinib.
- The results of the propensity score analyses conducted for the assessment of the clinical effectiveness were not implemented in the economic model. Furthermore, the analysis was based on PFS, an outcome not specified in the NICE final scope.
- The assumption of 5-year waning of utility after progression is unclear.
- No relationship between time on treatment and clinical effectiveness or HRQoL was modelled.
- No reduced mortality rate with selumetinib was modelled, despite the disease modifying nature of treatment with selumetinib and possible impact on mortality.
- The health state utility values and the caregiver disutilities used in the model are highly uncertain.
- The analysis includes only a limited number of cost items, and costs that are potentially relevant in relation to patient and symptomatic management were excluded.

Areas of uncertainty: The following areas of uncertainty were identified by the ERG:

- The size of the total population eligible for selumetinib might be bigger than indicated in the CS.
- Participants of SPRINT Phase II Stratum I were recruited in the USA which might limit the generalisability to patients in the UK.
- The ERG considers that the cost effectiveness results are subjected to substantial structural uncertainty since it is unclear whether the structure of the economic model is appropriate to model the natural progression of the disease. NF1 and PN are heterogenous and the evidence provided by the company suggests that disease progression, including PN growth rate, varies with age. Besides age, disease characteristics like PN volume or number of PN-related morbidities are expected to be treatment effect modifiers. All these associations are not captured by the current model, and while a patient-level model might capture some of them, it is unknown what the impact on the cost effectiveness estimates would be. A second source of structural uncertainty relates to the modelling of PFS. This seems inappropriate in general. For the selumetinib arm applying a constant annual probability of progression seems too simplistic, is not well justified and there is no possibility to change this in the model. Also, despite the evidence presented by the company suggesting otherwise, there is no PFS modelled in the BSC arm: patients are assumed to remain in the progressed disease health state. A full parametric modelling in the selumetinib arm and including PFS in the BSC arm (followed also by a full parametric modelling) should resolve some of the structural uncertainty, which in turn will be "replaced" by parameter uncertainty. Given the lack of data, this "new" parameter uncertainty is expected to be large, however, it should be assessed by a standard probabilistic sensitivity analysis (PSA). It is unknown what the impact of an alternative modelling of PFS on the cost effectiveness estimates would be but including PFS in the BSC arm is expected to increase the ICER.

- Despite the disease modifying nature of treatment with selumetinib and possible impact on mortality, no reduced mortality rate with selumetinib is modelled. If there were evidence available that could be used to model a possible reduction in mortality with selumetinib, this is expected to decrease the ICER.
- The ERG considers that the utility values included in the model are associated with a substantial amount of uncertainty as they are not based on measurements of HRQoL directly from patients/carers, it is unclear how well members of the general population were able to conceptualise this rare disease based on vignettes and it is unclear how the length of the descriptions and use of bolding would have affected the use of heuristic shortcuts and focussing effects on respondents. HRQoL data from patients/carers is required to better understand the impact of the condition on HRQoL and quantify the treatment effect in terms of utility. Data from carers in this population is also required to understand the disutility associated with caring.
- Another major uncertainty in the HRQoL submission is how progression and discontinuation impact utility. The assumption of a linear decline in utility over 5 years after progression is unsupported by evidence and unreflective of the health state vignette used to describe a progressive state. The model also assumed that discontinuation had no direct impact on utility, which does not seem realistic given that all patients receiving BSC are assumed to experience progressive disease.
- An important source of uncertainty relates to the inclusion of only a limited number of cost items, and exclusion of potentially relevant cost items in relation to patient and symptomatic management. As such, the analysis does not provide a comprehensive overview of relevant costs. There is no data available to inform health care resource use for patients treated with selumetinib, but it is likely that patient and symptomatic management costs will be reduced in these patients. Therefore, the exclusion of these costs may be a reason to interpret the cost effectiveness results as conservative estimates.

1.10 Summary of exploratory sensitivity analyses undertaken by the ERG

The following changes were made by the ERG to the company base-case:

1. The ERG prefers using a caregiver disutility equal to 0.07 instead of assuming that the impact of caring was equivalent to the impact of moving from stable to progressive disease for patients ([redacted]).
2. The ERG prefers assuming that the carer disutility will be applied to one caregiver instead of 1.4 given that there is no evidence that more than one caregiver is required in this population, and this is commonly assumed in previous NICE appraisals which have included caregiver disutilities.
3. The ERG prefers assuming a waning of utility after progression over 1 year instead of 5 years as utility was assumed to only take 1 year to increase to the on-treatment utility upon treatment initiation and no evidence was provided as to why the reverse process upon progression should take 5 years. Additionally, the vignette used to estimate a utility value for the progressive state describes a situation where the lump (PN) is growing, and no treatment is received. This already applies at the time of progression.
4. The ERG prefers assuming four MRIs per year for selumetinib instead of two, in line with clinical expert opinion obtained by the company.

The results from the ERG deterministic base-case are shown in Table 1.9. Overall, selumetinib costs an additional [redacted] for a QALY gain of [redacted], resulting in an ICER of £134,410 per QALY gained compared to BSC. The changes which had the largest impact on the ICER were using a caregiver disutility equal to -0.07 and assuming a waning of utility after progression over 1 year.

Table 1.9: ERG base-case results, discounted

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	134,410

Based on electronic model with ERG preferred assumptions
BSC = best supportive care; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

The ERG PSA yielded an ICER of £127,067, which is in line with the deterministic ICER. When plotted on the CE-plane, [redacted]. Based on these, the cost effectiveness acceptability curve (CEAC) was derived and at the threshold ICER of £100,000 per QALY gained, the probability that selumetinib is cost effective compared to BSC was [redacted]%. The ERG scenarios which had the largest impact on results were assuming alternative rates of progression, the length of the maximum duration of selumetinib treatment, assigning utilities to patients and to parents/caregivers and using 1.5% discount rates on costs and health effects.

2. BACKGROUND

2.1 Introduction

This chapter presents an overview of type 1 neurofibromatosis (NF1)-associated plexiform neurofibroma (PN) and its management. The content of this chapter is based on relevant literature, clinical information obtained by the Evidence Review Group (ERG) and information presented in the background sections of the company submission (CS).[1] For additional information on the aetiology, epidemiology, health impact, prognosis and management of type 1 neurofibromatosis-associated PN, please see pages 35 to 57 of the CS.[1]

2.2 Description of health problem

2.2.1 Disease overview

NF1 is a rare, complex and incurable disease in which symptoms manifest in early childhood and continue into adulthood.[2] Being a genetic disorder, the condition is heritable and may affect multiple members of the same family; however expression is highly heterogenous and can affect patients differently, even those with identical mutations.[2] Approximately one quarter of patients with NF1 go on to develop non-malignant peripheral nerve sheath tumours known as PN.

2.2.1.1 Neurofibromatosis type 1

Approximately 80% to 85% of NF1 patients are diagnosed by the age of six, with the vast majority (95%) being diagnosed by the age of eight years. Symptoms manifest across multiple organ systems, and can affect the nervous system, skin, bones and eyes.[3-6] In addition, individuals with NF1 have an increased risk of developing certain forms of cancer (including malignant peripheral nerve sheath tumours (MPNSTs), brain tumours, gastrointestinal stromal tumours, breast cancer, and leukaemia) as well as cognitive impairments, learning disabilities and mental health disorders.

2.2.1.2 Plexiform neurofibroma

Characteristics

PNs are non-MPNSTs that occur in approximately 25% of patients with NF1. They can occur anywhere in the body and may cause substantial morbidities due to their invasiveness and size, with tumours of over four litres recorded in paediatric patients.[7]

PN primarily affect the paraspinal region (31%), head and neck (31%) and extremities (25%) and may be confined and nodular or may involve multiple body regions.[8-10] Spontaneous resolution is rare, and as a result they usual persist throughout a patient's lifetime.[7, 11] The majority of PN are symptomatic and are typically associated with morbidities such as pain, disfigurement, and difficulties with physical functioning (see Section 2.2.5).

Current treatments

The only existing treatment effective at reducing or removing PN tumours is surgery.[9, 12] As PN are large and invasive, they present many difficulties in terms of surgical resection, and as a result approximately half of all patients with NF1 PN are considered inoperable (defined as PN which cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity).[13, 14] PN that have not been completely removed may grow back, and even PN which have been completely resected may recur in paediatric patients.[9, 15, 16]

2.2.2 Epidemiology

The CS reports a figure of 37 paediatric patients with NF1 and PN within the UK for which selumetinib is indicated. These values were derived from taking the total number of admissions of neurofibromatosis in patients aged 3 to 17 years (n=538)[17] and subtracting the proportion of these patients who 1) do not have PN (calculated at 75%),[18, 19] 2) who have asymptomatic PN (calculated at 45%),[20] and 3) have symptomatic but operable PN (calculated at 50%).[13, 14] The CS report references several studies from which the above prevalence data were sourced.[13, 14, 18-20]

ERG comment: The CS states that the number of patients for which selumetinib treatment is indicated may slightly overestimate the number of patients with NF1, given that the total number of admissions of neurofibromatosis would also include patients with NF2 and schwannomatosis. The source of this data reported subgroup admissions according to age (1 to 4 years, 5 to 9 years, 10 to 14 years, 15 years, 16 years, and 17 years).[17] Pooling data from age 5 to 17 years gives a total of 480 neurofibromatosis admissions, with an additional 116 patients admitted between age 1 to 4 years. The CS includes half this number of admissions (n=58) to give a final estimate of 538, which is likely appropriate.[1]

The ERG has identified a number of issues with the proportional values reported in Table B1 of the CS.[1] Specifically, the Table references a study by Nguyen et al. 2012 regarding the estimated proportion of paediatric NF1 patients who have symptomatic PN; however, background text within the study refers to a previous study (Nguyen et al. 2011 from which this value was derived (*"Recent studies revealed that 55% of PNs in childhood are symptomatic"*).[18, 20] As such, data reporting a 55% prevalence of symptomatic PN in paediatric NF1 patients was sourced from Nguyen et al. 2011 and not Nguyen et al. 2012 as stated.[18, 20] Within this study, the authors reported that of the 37 children with PN, 17 were symptomatic and 20 were asymptomatic, and thus the proportion of children with symptomatic PN was 46%.[18]

The authors of Nguyen et al. 2011 reported the proportion of paediatric NF1 patients who have PN (37/65 patients; 57%).[18] Therefore, the proportion of patients with NF1 who have PN is not 25%, as reported in Table B1 of the CS, but 57%.[1] Furthermore, the authors referenced Boulanger et al. 2005, stating that *"a previous study reported a much lower prevalence (24.7%) of PNs in children with NF1. However, in that study, only brain MRI* [magnetic resonance imaging] *was performed in a subset of patients"*.[18, 19] The authors go on to state that *"…it is likely that only symptomatic or visible PNs were diagnosed, and therefore the prevalence of 25% of PNs is in concordance with the prevalence of 26% of symptomatic PNs in the present study"*.[18]

Based on the cited studies, the ERG revised Table B1 to reflect the above, see Table 2.1. As is apparent, when using data from Nguyen et al. 2011 regarding the proportion of paediatric NF1 patients with PN (57%), and the revised data regarding the proportion of those patients who are symptomatic (46%), the estimated number of eligible patients has almost doubled from 37 to 70, see Section 7.2 for a discussion of the impact on the budget impact analysis.[18] It is therefore possible that approval by NICE based on the licenced indication may result in a higher proportion of patients with NF1 and PN being eligible/considered for selumetinib treatment.

Table 2.1: Total eligible patient population for selumetinib in England

Population	Estimated proportion		Estimated number		Source
	CS	ERG	CS	ERG	
Total population aged 3 to 17 years in England	-		10,140,338		Office for National Statistics, mid-2020[21]

Population	Estimated proportion		Estimated number		Source
	CS	ERG	CS	ERG	
Total number of admissions of neurofibromatosis (aged 3 to 17 years)	-		538		Hospital Episode Statistics - Primary diagnosis: 4-character table, neurofibromatosis (non-malignant) Q85.0, 2019-2020; assumed mostly NF1[17]
Proportion of paediatric patients with NF1 who have PN	25%	57%	135	306	CS: Nguyen et al. 2011 and Boulanger et al. 2005 (mean average taken)[18, 19] ERG: Nguyen et al. 2011[18]
PN which are symptomatic	55%	46%	74	140	CS: Nguyen et al. 2012 (upper end of range taken for a conservative estimate)[20] ERG: Nguyen et al. 2011[18]
Proportion of PN which are inoperable	50%		37	70	Waggoner et al. 2000[14], Serletis et al. 2007 (Mean average taken)[13]
Total eligible patient population	**-**		**37**	**70**	**Calculated from above**

Based on Table B1.2 of the CS[1]
CS = company submission; ERG = Evidence Review Group; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibroma

2.2.3 Aetiology

NF1 is a genetic disorder that produces lifelong phenotypic variability and almost complete penetrance. PN occur in around a quarter of patients with NF1[1].

Several phenotypes are linked to increased incidence and progression of PN. Studies have shown that patients with non-mosaic large NF1 gene microdeletions experience high PN burden. In particular, mutations in ANRIL, SUZ12 and ATM genes negatively affect the formation and number of PNs and their progression (both malignant and non-malignant).[22]

2.2.4 Pathogenesis

Children with NF1 PN experience uncontrolled and unpredictable growth of PN, with periods of rapid growth followed by periods of slow or no growth.[3, 7] A number of PN clinical trials have used the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria to define PN volume decrease and increase, i.e. improvement and progression. PN volume increase is defined as a 20% or greater increase in tumour volume from baseline. Conversely, PN volume decrease is defined as a 20% or greater decrease in tumour volume from baseline.

The majority of paediatric NF1 PN patients experience increases in tumour volume, with one study reporting 86% of patients underwent a ≥20% increase in tumour volume, with the median PN volume change from baseline being 109%.[7] Few patients experience spontaneous decrease in volume, with one study reporting that only 9% (10/113) of patients experienced spontaneous tumour volume reduction over the full follow-up period (ranging from 3 to 10.3 years). Only three of these patients were younger than 18 years of age.[23]

ERG comment: The CS states that in the study reporting spontaneous tumour reductions, only three of the patients experiencing such reductions were younger than 18 years of age.[23] The percentage decrease

from maximum volume were 20.5%, 21.3% and 13% for these patients, respectively. Therefore, only two patients experienced PN volume decrease based on REiNS criteria as specified within the CS.[1]

2.2.5 Clinical features

2.2.5.1 Pain morbidities

Pain is a frequent symptom of NF1 PN and can range in severity from minor sensory alteration to complete myelopathy.[8] Pain was identified as a PN-associated symptom in 30% to 41% of patients within two studies, most commonly resulting from contact with or pressure applied to the PN.[18, 24] In one study, a third of paediatric NF1 PN patients (20/60) were taking pain medication regularly, the majority of whom were taking prescription pain medications or a combination of over-the-counter and prescription pain medications. Despite regular pain medication use, 14/15 (93%) of adolescents reported that pain was still interfering with daily functioning to some degree.[25]

2.2.5.2 Motor morbidities

PNs which restrict the range of motion of a joint or causing pain during movement may lead to impaired motor function in patients with NF1 PN. In serious cases, growing spinal and paraspinal neurofibromas can put pressure on spinal nerves, leading to significant muscle weakness and disability.[26]

In one study, the incidence of PN-related motor morbidities doubled from 11 to 22 between baseline and maximum assessment.[7] Those PNs which resulted in motor dysfunction generally had larger volumes compared to those that did not (median 818 ml vs. median 238 ml), suggesting that the growth of PN over time can lead to increasing severity of motor dysfunction.[7]

ERG comment: The referenced article highlighted the potential for significant muscle weakness and disability resulting from spinal and paraspinal neurofibromas is a letter to the editor involving a single patient, suggesting that such occurrences are very rare.[26]

The values provided in the CS regarding PN volumes (818 ml vs. 238 ml) were specific to patients at baseline.[1] At maximum follow-up, patients experiencing motor dysfunction had median PN volumes of 1,240 ml compared to 664 ml in those without motor dysfunction, a respective increase of 422 ml and 426 ml respectively. This suggests that total volume is a more important contributing factor to motor morbidities rather than the rate of PN growth. Further, the source of data is a single observational study that included 41 participants, and thus certainty of evidence is very low.[7]

2.2.5.3 Airway morbidities

Many studies have demonstrated serious morbidities following growth of PN near airways, including airway obstruction, which requires patients to undergo tracheostomies and in some cases leads to death.[9, 13, 27] The growth of PN near airways can also cause morbidities such as sleep apnoea, which may be treated with continuous positive airway pressure (CPAP).[28, 29] PNs that compromise airways or cause pulmonary dysfunction are predicted to occur in 5 to 7% of paediatric NF1 PN patients.[29]

2.2.5.4 Bladder and bowel morbidities

Limited data are available informing incidence and prevalence of bladder and bowel morbidities in paediatric NF1 PN patients. The CS provides general information regarding these morbidities, stating that PN in the region of the bladder and bowel can impede the function of these organs, causing burdensome symptoms such as incontinence. Further, growth of these PN can result in more severe complications such as bowel obstruction or blood in the urine.[7, 30]

ERG comment: As specified within the CS, PN can result in complications such as bowel obstruction and blood in the urine. Specifically, the study by Gross et al. 2018 reported one case of PN-related urinary incontinence and five cases of PN-related bowel obstruction.[7] The CS states that these complications develop as a result from PN growth; however the author states that *"only weak associations with relatively small differences in size and growth were found between PN size or growth rate and the presence or absence of vision, airway, bowel or bladder morbidities, and none of these were statistically significant"*.[7]

2.2.5.5 Vision morbidities

PN growth around the eye can prevent the eye from achieving normal visual acuity (amblyopia) and can cause significant morbidity, including eye pain, drooping of the eyelid (ptosis) and severe protrusion of the eye (proptosis).[31] PN involving the eyelid, orbit, periorbital and facial structures can cause significant visual loss which in some cases may require enucleation (removal of the eye).[32] Orbital and periorbital PN can also result in the development of glaucoma and optic nerve disease due to compression, especially if the PN grows rapidly.[31]

2.2.5.6 Disfigurement

The growth and development of PN can result in severe disfigurement. This frequently occurs in children with orbital and periorbital PN in which ptosis, proptosis, cheek deformities and asymmetry of the eyelids can cause significant alterations in appearance.[31] In addition to the negative impact on quality of life (social and physical functioning and self-esteem), such disfigurement can also contribute to functional morbidities such as vision loss.

One study determined that disfigurement was the second most common PN-associated morbidity in paediatric NF1 PN patients, with an incidence of 32.9%.[33]

ERG comment: The referenced citation by Yang et al. 2021 reporting the incidence of disfigurement in paediatric NF1 PN patients is only available as a conference abstract.[33] The abstract included data from 82 patients, provided no definition of disfigurement, and provided no information regarding risk of bias or funding. It is therefore unclear if this figure accurately represents the true incidence of disfigurement in paediatric NF1 PN patients.

The CS states that [redacted].[30] Although this suggests that disfigurement is not limited to paediatric NF1 PN patients, incidence of disfigurement in adults is outside the scope of the submission.

2.2.6 Diagnosis

Diagnosis of NF1 were previously based on National Institutes of Health (NIH) criteria developed at the 1988 NIH Consensus Development Conference.[3, 34] However, these have recently been reviewed and revised by the International Consensus Group on Neurofibromatosis Diagnostic Criteria which were published in 2021 and are generally accepted by clinicians in the United Kingdom (UK).[35]

The revised diagnostic criteria list six clinical features and one genetic feature; specifically, the presence of a heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells. For individuals without a parent diagnosed with NF1, two or more of these criteria are required for diagnosis; for individuals with a parent diagnosed with NF1, only one criterion is required.[35]

For diagnosis of PN in individuals with confirmed NF1, PN must also be identified. The majority of visible PN may be diagnosed when they first appear or are identified following annal routine physical examination, however approximately 20% of PN are not visible and require imaging (using MRI) to confirm diagnosis.[7, 36]

ERG comment: Regarding the revised criteria for diagnosis of NF1, the CS states that *"these criteria are generally accepted and will be used by clinicians in the UK"*.[1] However, no reference was provided to support this statement.

2.2.7 Prognosis

Patients with NF1 have a higher mortality rate and lower life expectancy than the general population due to an increased lifetime risk of developing certain types of cancer.[37-42] In addition, patients with NF1 PN have been shown to have a higher mortality rate than the general NF1 patient population, with one study demonstrating a 3.2% increase in mortality when comparing patients with symptomatic PN with non-PN NF1 patients (P=0.024).[9]

The development of MPNSTs may contribute to this increase in reported mortality. MPNSTs are thought to be associated with PN, with the risk of developing an MPNST increasing 20-fold in areas with existing PN.[43] It is unclear whether treatment which reduces or removes PN modifies the risk.

2.2.8 Impact on patients' health-related quality of life (HRQoL)

2.2.8.1 Paediatric patient HRQoL

An observational study published in 2019 reported results from 140 paediatric patients with NF1 PN who completed Patient-Reported Outcomes Measurement Information System (PROMIS) and Neuro-quality of life (QoL) questionnaires. Compared to the general population, children reported worse scores on eight of ten domains, including meaning and purpose, depression, anxiety, psychological stress experiences, peer relationships, and physical function/mobility. The two domains in which no statistical difference was observed were pain and fatigue.[42]

Several studies have demonstrated an association between PN and negative impact on HRQoL due to the burden of morbidities.[25, 42, 44] Physical functioning impairments such as motor, airway, vision or bowel and bladder morbidities may limit patient participation in physical activities with peers.[42, 44] Children with NF1 PN may be unable to participate in educational and social activities due to the impact of PN-associated morbidities, often resulting from increased absences due to medical treatment and hospitalisation.[24]

Pain is directly associated with poorer HRQoL in paediatric NF1 PN patients. Wolters et al. 2015 demonstrated an association between greater pain interference and increased socialisation difficulties and poorer overall HRQoL.[25] One additional study reported that as a result of pain, patients felt a need to be careful during physical exercise, or to limit their participation in physical activity.[24]

Physical disfigurement may also have a significant negative impact on patients' wellbeing. This can occur both through increased self-consciousness and concerns around body image and stigma as well as through bullying.[44-46] Uncertainty surrounding the clinical course of the disease, and the prospect of further disease progression and increasing morbidity may also result in increased anxiety.[42] The increased prevalence of anxiety and depression is exemplified within one study, which reported that 10% of patients were using antidepressants.

The impact of NF1 PN on individual patients' psychological health and wellbeing is demonstrated in a case report, in which an individual specified that they had been using antidepressants since the age of 17 years and had been suffering from panic attacks since age 7 years. The patient stated that such panic attacks were usually triggered by anxiety about the future and progression of the disease. This patient had become bedbound by their early twenties due to nerve compression and was experiencing suicidal ideation.[26]

ERG comment: The study by Jensen et al. 2019 described the negative impact on paediatric NF1 PN patients' ability to participate in school, stating that *"participants described missing school frequently due to medical appointments and pain. A subset also spoke about needing modifications to participate in different aspects of school"*.[24] The ERG cannot identify text within the study supporting the proceeding statement that such limitations have *"a substantial emotional impact on both the child and their family"*. Although such impact is likely, this statement is an extrapolation of study results and represents the conclusion of the CS authors. For clarification, the citation should be added prior to this statement.[26]

The CS provides an in-depth analysis of a case report in which one patient discussed their depression and subsequent suicidal ideation. Although relevant, case reports should be considered to be insufficiently robust sources of evidence to support more general statements regarding a disease.

2.2.8.2 Family and Carer HRQoL

In addition to the effect on QoL for the paediatric patient, NF1 PN can also have a significant burden on families and carers. Most children with NF1 PN require support with their daily activities throughout childhood, and this need for support may extend into adulthood. In addition, as the condition is heritable, other family members may also be affected and further increases the burden.[10] A cross-sectional study conducted within the United States of America (USA) found that approximately 50% of NF1 PN carers reported a burden ranging from mild to severe.[47]

One study has reported the ways in which parents and carers provide support, including managing and monitoring patients' symptoms, supporting with daily activities, and providing educational, emotional and physical support.[45]

[redacted][1]

The burden of caregiving can also have an emotional impact on parents and carers. This can manifest as anxiety due to the uncertainty surrounding PN growth and PN-associated morbidities,[26, 45] as well as anxiety with regards to the physical, emotional and psychological health of the children they care for and concerns about not knowing what care is best for their child.[42, 44, 48]

In addition, caring for a child with NF1 PN can impact the daily activities and social lives of carers.[45] Of 95 carers in one study, an average of 17.2% of regular daily activities were hindered by providing care for their child with NF1 PN.[47] Caring for children with NF1 PN can also have a negative impact on carers' careers. Some carers described the difficulty of fitting in numerous medical appointments around their work. Other carers, particularly those looking after children with more complex needs, reported that it was impossible for them to have a career because of the care needs and appointments

related to their child's condition. Employed carers of children with NF1 PN reported missing an average of 6.9% of their working hours and an average reduction of 17.3% of on-the-job effectiveness (presenteeism), contributing to an average reduction of 22.3% of work productivity in the last week.[47]

ERG comment: The CS includes a comprehensive section focused on adult patient HRQoL. Considering that NF1 is incurable, this is an important consideration as the disease progresses into adulthood. However, in line with the NICE scope, the submission is limited to paediatric patients (age 3-17 years) and thus for this indication adult HRQoL is of lesser relevance, see Section 3.

The majority of data from this section are derived from a poster abstract which included 95 parents and caregivers of paediatric patients with NF1 PN.[47] This abstract reported very limited data, did not provide any information regarding study methods and was funded by Merck Sharp & Dohme Corp. As a result, there is uncertainty regarding whether the observed effects truly reflect those experienced in real world settings.

Regarding the impact of caregiving on the careers of carers, the CS states that *"employed NF1 PN carers in the US (n=95) reported missing an average of 6.9% of their working hours (absenteeism) and an average reduction of 17.3% of on-the-job effectiveness (presenteeism)"*.[1] The cited abstract by Yang et al. 2021 specified that of the 95 included carers, a total of 56 were employed and working in the 7 days prior to completing the survey. The text should reflect this reduced number.[47]

The CS states that *"unaffected siblings will also be impacted and may find it difficult to understand the situation"*.[1] While this is plausible, there is no reference provided to support this statement. Furthermore, the highlighted text above provides no reference with regards to [redacted].

2.3 Current service provision

The CS states that there are no National Institute for Health and Care Excellence (NICE) guidelines or guidance documents for the treatment and management of NF1 PN; however, information published on the National Health Service (NHS) website states that children with NF1 should have a comprehensive examination once a year, including skin examination for PN, and that patients who develop complex problems are referred to one of two specialist treatment centres within the UK.[49] Guidelines developed in 2007 by the UK Neurofibromatosis Association Clinical Advisory Board state that management of NF1 patients should be focussed on age-specific monitoring of disease manifestations and patient education. These guidelines reflect the above NIH information, in that all paediatric patients with uncomplicated NF1 should be assessed once a year.[3]

The current clinical care pathway for patients with NF1 PN involves initial surgical assessment followed by either surgery to achieve complete resection (if the PN is deemed operable), potential surgery if partial resection is expected to be achieved, or no surgery (if the PN is deemed unsuitable for surgery based on clinical opinion). Irrespective of whether surgery is performed or not, this is followed by established clinical management. Further information specific to care pathways for individuals with inoperable PN is presented on page 55 of the CS.[1]

Clinical management of NF1 PN is limited because of their unsuitability for treatment with traditional antineoplastic agents such as radiotherapy and chemotherapy due to the risk of malignant transformation.[37] There are currently no available pharmacological treatments to cure, prevent or reduce

the volume of inoperable PN. Although a number of drugs have been evaluated in this population, few have shown clinical benefit, and none have been approved for use in patients with NF1 PN.[1]

Patients with NF1 PN must rely on palliative care and symptomatic management. Between 33% and 44% of NF1 PN patients receive treatment for the management of pain, including prescriptions for opioid painkillers.[25] Continued pain interference is frequently reported, and long-term pain medication has known adverse events, particularly for opioid medications, which are associated with risks of substance abuse, addition, bone fracture and cardiovascular events.[50] Psychological support may also be required to manage anxiety and depression. Further information regarding symptom management of NF1 PN can be found on pages 55 to 56 of the CS.[1]

ERG comment: The CS states that *"although a number of drugs have been evaluated in this population, few have shown clinical benefit, and none have been approved for use in patients with NF1 PN"*.[1] No reference has been provided for this statement. The CS does not specify what these *"few"* treatments which have shown a clinical benefit are and how they compare to selumetinib.

2.4 Description of treatment under assessment

Selumetinib is a potent, selective, small molecule inhibitor of MEK1/2 indicated for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.[32, 51, 52] MEK1/2 are key components of the RAS/RAF/MEK/ERK signalling cascade, the inhibition of which is thought to prevent PN growth and promote PN shrinkage by reducing cell proliferation and preventing abnormal cell survival.

The CS provides a suggested modified treatment pathway,[1] in which patients with inoperable or partially resectable PN receive selumetinib treatment in conjunction with established clinical management after surgery (see Figure 1 of the response to the request for clarification).[32, 51, 53]

3. CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final agreed NICE scope,[54] is to evaluate the benefits and costs of selumetinib within its licensed indication for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above for national commissioning by NHS England (NB: conditional licensing, Selumetinib was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2021.[53]

The final NICE scope outlines the agreed population, intervention, comparators and outcomes for the appraisal.[54] The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the NHS and PSS and value for money.

3.2 Adherence to the decision problem

Table 3.1 presents a summary of the decision problem (DP) as set out in the NICE scope[54] and the company's adherence to this (based on information presented in Table 1 of the CS).[1]

Table 3.1 Adherence to the agreed decision problem, as reported in the CS

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale for variation from scope	ERG comment
Population	Children aged three years and over with symptomatic and inoperable PN associated with NF1	Children aged three years and over with symptomatic and inoperable PN associated with NF1	N/A	In line with NICE scope. However, please see comments in Section 3.3.1 regarding the identified evidence
Intervention	Selumetinib	Selumetinib	N/A	In line with NICE scope
Comparator(s)	Established clinical management without selumetinib	Established clinical management without selumetinib, including pain management (prescription and over-the-counter painkillers)	N/A	In line with NICE scope
Outcomes	• Complete and partial response rate • Growth rate of PN • Disfigurement • Physical functioning • Visual function • Airway functioning • Bowel and bladder continence • Pain • Adverse effects of treatment • HRQoL (children)	In addition to those detailed in the final scope, the following relevant outcomes will be presented: • Duration of response • PFS • Time to progression • Global impression of change	Additional outcomes from the SPRINT Phase II Stratum I trial (duration of response, progression free survival, time to progression and global impression of change) are relevant for assessing the efficacy of selumetinib	In line with NICE scope with four outcomes added. Please see Section 3.3.4 for further details
Cost to the NHS and PSS, and Value for Money	Cost-effectiveness expressed in terms of incremental cost per QALY The time horizon for estimating clinical and cost effectiveness	The economic analysis has been conducted in line with the NICE reference case	N/A	In line with NICE scope

	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs should be considered from an NHS and PSS perspective			
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service[a]	Whether there are significant non-health benefits Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS The potential for long-term benefits to the NHS of research and innovation The impact of the technology on the overall delivery of the specialised service Additional staffing and infrastructure requirements, including training and planning for expertise	All points have been considered within this submission	N/A	All point were considered in a narrative, but potential benefits were not quantified
Special considerations, including issues related to equality	No special considerations identified	No special considerations identified (see Section 5 of the CS)	N/A	In line with NICE scope

Based on Table A1 of the CS[1]

[a] Details of the impact of selumetinib beyond direct health benefits and on the delivery of the specialised service have been reported in Section E as per the submission template

CS = company submission; ERG = Evidence Review Group; HRQoL = health-related quality of life; N/A = not applicable; NHS = National Health Service; NF1 = type 1 neurofibromatosis; NICE = National Institute for Health Research; PFS = progression free survival; PN = plexiform neurofibroma; PSS = personal social services; QALY = quality adjusted life year

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The DP addressed in the CS is in line with the NICE final scope, i.e. *"children aged three years and over with symptomatic and inoperable PN associated with NF1"*.[1, 54]

However, as detailed in Section 4.2.1, the main source of data was one study, namely Stratum I of Phase II of the SPRINT study.[11]. This study included patients aged 2 to 18 years. However, as shown in Table C9 of the CS, [redacted], i.e. it is unlikely that this has a major impact on the findings of this study.

As discussed in Section 4.2.1, the ERG reassessed the studies identified in the CS and considers two further studies relevant for inclusion in this report.[55, 56]

3.3.2 Interventions

Selumetinib was administered with a dose of 25 mg/m^2 body surface area (BSA) twice daily (BID), as detailed in Table A3 of the CS and confirmed in response to the request for clarification.[1, 53]

3.3.3 Comparators

The final scope issues by NICE defined the comparator of interest as *"established clinical management without selumetinib"*.[54] The DP addressed by the company amended that definition by adding *"…including pain management (prescription and over-the-counter painkillers)"*.[1] Other potential comparator treatments were mentioned in the CS but not explored, as discussed in Section 5.3.3.7.2 of this report.

3.3.4 Outcomes

In addition to the 10 outcomes defined in the final scope issued by NICE (see Table 3.1), the DP addressed by the company included four additional outcomes, namely duration of response, progression-free survival (PFS), time to progression (TTP), and global impression of change (GIC).[1]

Results for duration of response, TTP, and GIC are not presented in detail, see Section 4.2.4.1.11 for prompts to the respective sections of the CS. However, as PFS has been used in a propensity score analysis (see Sections 4.1.5 and 4.2.4.3), results are presented in Section 4.2.4.10.

3.3.5 Cost to the NHS and PSS, and value for money

The CS includes cost effectiveness analyses in which results presented in the form of incremental costs per quality-adjusted life years (QALYs) over a lifetime time horizon, with the impact of treatment on the health-related quality of life (HRQoL) of patients and caregivers included in the analysis. Cost effectiveness analysis. Costs calculated according to the National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and QALYs discounted at 3.5%. In general, the NICE scope and reference case were followed when assessing the costs of selumetinib to the NHS and the value for money it provides.

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix 1 (Section 17.1) of the CS provided details of the systematic literature searches used to identify clinical evidence.[1] Database searches were conducted between January and February 2021. A summary of the resources searched are provided in Table 4.1.

Table 4.1: Resources searched for clinical evidence. January/February 2021.

Resource	Host/Source	Date Range	Date searched
Databases			
Embase	Ovid	1974-2021/01/25	26.1.21
MEDLINE & MEDLINE In-Process	Ovid	1946-2021/01/25	26.1.21
CDSR	Wiley	Up to 2021/01/Iss1	26.1.21
CENTRAL	Wiley	Up to 2021/01/Iss1	26.1.21
DARE	CRD	Up to 2015/04/Iss2	26.1.21
Conference Proceedings			
ISPOR (International & European meetings)		2018-2020	5.2.21
JGNC (Children's Tumor Foundation NF + European Neurofibromatosis)		2018	5.2.21
Children's Tumor Foundation NF		2019-2020	5.2.21
ESMO		2018-2020	5.2.21
ASCO		2018-2020	5.2.21
ISPNO		2018 & 2020	5.2.21
ASPHO		2018-2020	5.2.21
Clinical Trials Registries			
ClinicalTrials.gov			28.1.21
Additional searches			
Manual searches of materials provided by AZ			
Manual searches of the bibliographies of all relevant SLRs and (network) meta-analyses ([N]MAs) identified during the course of the review			

ASCO = American Society of Clinical Oncology; ASPHO = American Society of Pediatric Hematology/Oncology; AZ = AstraZeneca; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Disseminations; DARE = Database of Abstracts of Reviews of Effects; ESMO = European Society for Medical Oncology; ISPNO = International Symposium on Pediatric Neuro-Oncology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; JGNC = Joint Global Neurofibromatosis Conference; MA = meta-analysis; NF = neurofibromatosis; NMA = network meta-analysis; SLR = systematic literature review

ERG comment:

- The company searched a broad range of resources, including supplementary searches of conference proceedings and other relevant resources such a trials database, company records and the checking of references lists to identify additional studies not retrieved by the main searches. Individual strategies were well constructed and contained a combination of subject heading index and free text terms. Searches were clearly reported and reproducible.
- The ERG queried an error in the line combinations in the Embase search (Table 3, Appendix 1): Line #52 ("conference abstract" or "conference review").pt. was limited in line #53 to papers published between 1974 and 2018 (limit 52 to yr="1974-2018").[57] However, when the facet for excluded terms was combined in line #57, line #52 had been included in error, instead of just line #53, excluding all conference proceedings not just those published before 2018. The company clarified that this had been a transcription error resulting from the inclusion of an erroneous table and confirmed that the original strategy run on 26 January 2021 did include all conference abstracts published from 01 January 2017 onwards and provided a corrected copy of the search strategy (Table 1 of the response to the request for clarification).[53]
- The ERG noted a potential error in the Database of Abstracts of Reviews of Effects (DARE) search (Table 5, Appendix 1). Line #4 MeSH DESCRIPTOR Neurofibroma, appeared to have been combined in error in line #7 with terms for NF1, rather than in line #8 with terms for PN as had been done in the previous Medline, Embase and Cochrane searches. The company acknowledged this error at clarification and provided a corrected strategy confirming that no relevant studies had been missed (Table 2 of the response to the request for clarification).[53]
- The ERG queried a disparity between the number of conference results reported in the PRISMA diagram (Figure C1 of the CS, n=1,083) and in the searches reported in Table 6 of Appendix 1 (n=1,104). The company confirmed that the number recorded in the PRISMA diagram was accurate, the error occurred in the results reported in Table 6 of Appendix 1 and an amended version was provided (Table 3 of the response to the request for clarification).[53]
- At clarification the ERG queried the combination of terms for PN and NF1 in the condition facet of the search strategies.[57] Whilst the ERG agreed with the company response that this *"was suitably specific given the focus of the scope on NF1 patients with PN"*,[53] given the low number of a hits retrieved the ERG feels that a more sensitive approach may have beneficial. However, given the broad range of additional searches, it is unlikely that any key papers would have been missed.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 4.2.

Table 4.2: Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Paediatric (aged ≥3 and ≤18 years) and/or adult (aged >18 years) patients with inoperable NF1 PN	Paediatric and/or adult patients without inoperable NF1 PN, with NF1 but no PN, or with PN that can be completely resected.
Interventions/ comparators	• Selumetinib • Any intervention (including established clinical management) • No intervention	Any other intervention or emerging therapies, including symptomatic, supportive treatments (e.g., binimetinib, trametinib, carbozantinib, mirdametinib, pain management, tracheostomy) Interventions not considered to be 'emerging therapies' for NF1 PN (tipifarnib, sirolimus, Imatinib, PEG-interferon Alfa-2b, pirfenidone everolimus)
Outcomes	• Objective response rate • Complete response rate • Partial response rate • Stable disease • Progression free survival • Time to progression • PN volume change • Growth rate of PN • Effect on physical functioning • Effect on pain • Adverse events • Deaths • Discontinuations • HRQoL	No reported outcomes of interest
Study design	• RCTs • Interventional non-RCTs • Observational studies	Narrative reviews or economic evaluations
Publication type	Peer-reviewed journal articles, congress abstracts published in or since 2018, or letters (if they report primary research)	Non-peer-reviewed journal articles (e.g., editorials, commentaries, opinion pieces), book chapters, clinical guidelines, or congress abstracts published before 1st January 2018
Language restrictions	Publications with at least an abstract in the English Language	Publications without an abstract in the English Language

Based on Table C1 of the CS[1]

Note: SLRs or (N)MAs of relevant study designs were included at title/ abstract screening stage but excluded at the full-text screening stage

CS = company submission; HRQoL = health-related quality of life; MA = meta-analysis; NF1 = type 1 neurofibromatosis; NMA = network meta-analysis; PEG = pegylated; PN = plexiform neurofibromas; RCT = randomised controlled trial; SLR = systematic literature review

ERG comment: With the exception of the population (which included adult patients to broaden the scope of the search), the eligibility criteria appear adequate to retrieve studies to match the NICE scope.

The company was asked to clarify how many studies with abstract in the English language had been identified post-searches and how these were handled.[57] In response to the request for clarification, the company stated that *"the SLR did not identify any relevant studies with only the abstract in the English Language"*.[53]

4.1.3 Critique of data extraction

The CS states that data extraction was performed by one reviewer and data extracted into a pre-specified Microsoft Word table and was then checked by a second, independent reviewer.

ERG comment: Double data extraction by two independent reviewers with a third reviewer being involved to resolve disagreements on discrepancies that may arise, is largely recommended to reduce bias, and avoid error, e.g. in the Cochrane Handbook for systematic reviews of intervention.[58] Therefore, there is greater uncertainty on the veracity of the extracted data.

4.1.4 Quality assessment

Eight published studies met the inclusion criteria and were included in the systematic literature review (SLR).[11, 55, 56, 59-63] The company conducted quality assessments on two studies not identified in the clinical SLR[7, 64] and on the SPRINT Phase II Stratum I study[11] considered by the company to be of greatest relevance to the DP.[1] These critical appraisals can be found in Tables C13 to C15 of the CS.[1]

ERG comment: In questions A8 and A15 of the clarification letter, the ERG probed into why seven of the eight relevant clinical SLR studies were not included in the main body of the CS (which would warrant a quality assessment).[57] In the response to the request for clarification, the company provided no justification for this, but rather reiterated the relevance of these identified studies in the CS.[53] Section 4.2.3 of this provides further discussion on the critical appraisals included in the CS.

Furthermore, the company was asked to clarify the process of assessment for the three studies critically appraised in the CS.[57] In the response to the request for clarification, the company stated that *"quality assessments were conducted by one independent reviewer and verified by a second independent reviewer. Any discrepancies identified by the second reviewer was discussed by both individuals and if necessary, a third independent reviewer as enlisted to arbitrate the final decision."*.[53] It should be noted that this is not in line with best practice, e.g. the Cochrane Handbook states that at least two people should work independently on the risk of bias assessment as *"duplicating the risk-of-bias assessment reduces both the risk of making mistakes and the possibility that assessments are influenced by a single person's biases"*.[58]

4.1.5 Evidence synthesis

There is a lack of head-to-head trials comparing selumetinib to established clinical management. Therefore, in order to determine comparative effectiveness, non-randomised comparisons vs. external control data in the form of naïve comparisons were conducted between SPRINT Phase II Stratum I (NCT01362803; n=50),[11] an age-matched cohort from the National Cancer Institute (NCI) National History study of NF1 (NCT00924196; n=93),[7] and patients with progressive PN in the placebo arm of a randomised controlled trial (RCT) investigating tipifarnib in patients with NF1 PN (NCT00021541; n=29)[64]. Admittedly, differences across trials, e.g. in baseline patient characteristics, can impact results in a way that would lead to naïve comparisons producing biased estimates of treatment effects. Consequently, to explore the potential impacts of adjusting for baseline

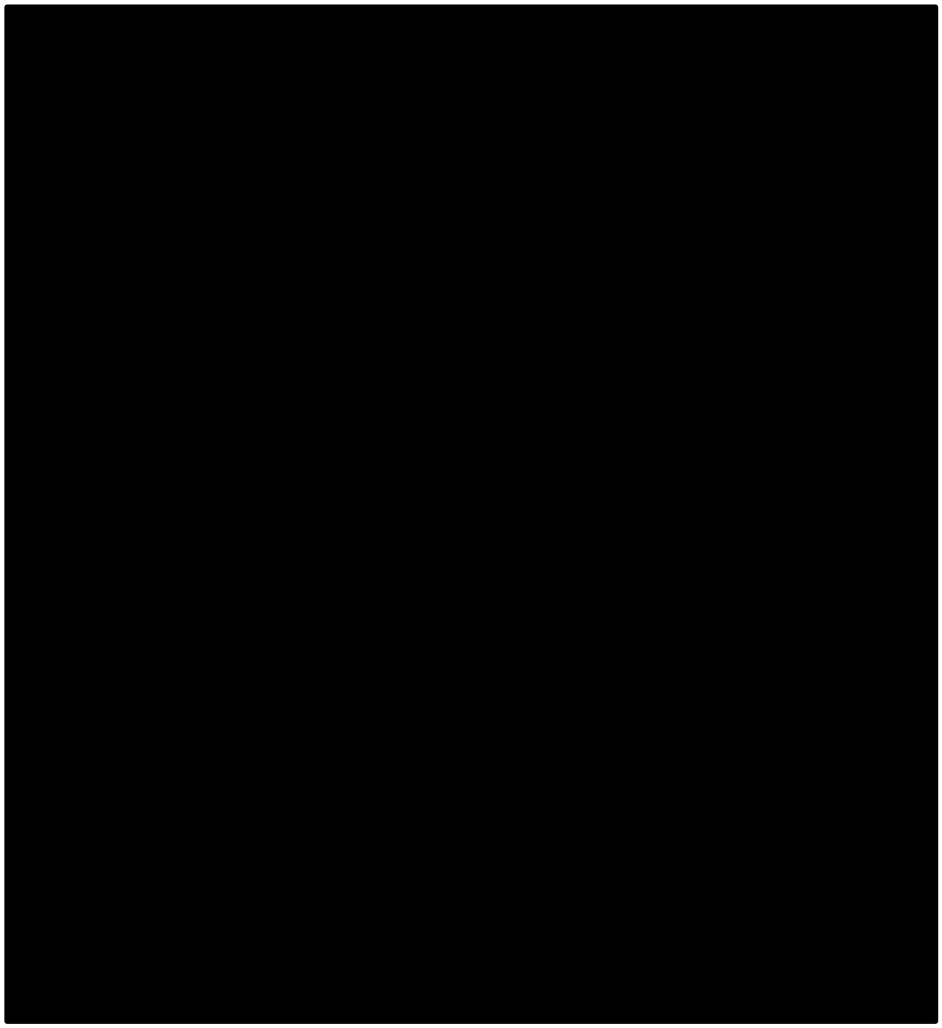
covariates across the study population, the company undertook propensity score analyses.[1] These analyses were based on the PFS data reported in the SPRINT clinical study report (CSR)[32] rather than data from Gross et al. 2020[11] as it presented the longest duration of clinical outcome follow-up data.[1]

ERG comment: In Figure C19 of the CS, 92 patients are reported to have formed the age-matched cohort from the NCI National History study, however in Table C9, the baseline patient characteristics data for 93 patients in the age-matched cohort was provided.[1] It is unclear if this discrepancy is due to missingness of data or an error in reporting.

4.1.5.1 Propensity score analysis patient eligibility

All patients (n=50) in the SPRINT Phase II Stratum I study were considered in the propensity score analysis. A small number of patients ([redacted]) who were included in the Natural History age-matched cohort were subsequently enrolled in SPRINT Phase II Stratum I, and patients with missing weight and height at first MRI assessment of target PN ([redacted]) were excluded from the Natural History arm of the comparison, leaving 65 patients in the Natural History age-matched cohort eligible for propensity score analysis, see Figure 4.1 for patient eligibility.

Figure 4.1: Propensity score analysis patient eligibility



Based on Figure C19 of the CS[1]
CS = company submission; MRI = magnetic resonance imaging; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibroma

4.1.5.2 Propensity score analysis methods

Three methods were used for propensity score matching/weighting (see Table 4.3 for baseline characteristics of matched sample pair):

1. Propensity score matching 1:1 (without replacement): Outcomes were directly compared between a callipher-matched sample of [redacted] from the SPRINT study and [redacted] from the Natural History study using a greedy matching algorithm.
2. Inverse probability of treatment weighting (IPTW): Each patient from the SPRINT Phase II Stratum I and eligible patients in the Natural History study were assigned a weight based on the inverse of the propensity score.
3. Propensity score matching 1:2 (with replacement): Matches were found for [redacted] from the SPRINT study based on [redacted] from the Natural History study. Weighting for patients was conducted in accordance with the method proposed by Ho et al. 2011 to get a sum of weights that is equal to the total number of unique patients in the matched analysis.[65]

Table 4.3: Baseline characteristics for all patients included in the propensity score analysis

Variable		Pre-matching/weighting			1:1 matching			Stabilised IPTW			1:2 matching		
		SPRINT ([redacted])	NH ([redacted])	Std. Diff.	SPRINT ([redacted])	NH ([redacted])	Std. Diff.	SPRINT ([redacted])	NH ([redacted])	Std. Diff.	SPRINT ([redacted])	NH ([redacted])	Std. Diff.
Sex n (%)	Female	[redacted]											
	Male	[redacted]											
Race n (%)	White	[redacted]											
	Other	[redacted]											
Age (years)	Mean, SD	[redacted]											
Weight (kg)	Mean, SD	[redacted]											
Height (cm)	Mean, SD	[redacted]											
Target PN volume (L)	Mean, SD	[redacted]											
Target PN location n (%)	Head/Neck/ Trunk	[redacted]											
	Trunk/Extremity/ Whole Body	[redacted]											

Based on Table C28 of CS[1]

CS = company submission; IPTW = inverse probability of treatment weighting; N = number of participants included in analysis; NH = Natural History Study; PN = plexiform neurofibroma; SD = standard deviation; Std. Diff = absolute standardised difference

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

As reported in Section 9.2 of the CS, the company's SLR identified eight studies (published in 25 papers) that met the eligibility criteria.[1] No eligible unpublished studies were identified. The study selection decisions are represented in Figure C1 of the CS. Summary details of the eight included studies and 25 associated publications are provided in Table C3 and bibliographic information for all papers is shown in Table 8 (Appendix 1) of the CS.[1] Further details of the eight eligible studies are presented in Tables 10 to 59 (inclusive) of the appendices.[1]

As presented in Table C3 of the CS,[1]all of the eight included studies were uncontrolled evaluations of selumetinib including four single-arm trials,[11, 59-61] two case series,[55, 56] one ongoing interventional study[62] and one individual case report.[63]

Table C3 of the CS provides details of participant characteristics for the included studies.[1] Seven of the eight studies recruited children and adolescents (up to 19 years of age) with NF1 and inoperable PN.[11, 55, 56, 60-63] Three of these (all single-arm trials) relate to different phases of a common evaluation, the SPRINT study (NCT01362803).[11, 60, 61] Phase I involved a dose escalation study to establish the maximum tolerated dose of selumetinib in children with NF1 and inoperable PN with potential or actual PN-associated symptoms.[60] Phase II evaluated efficacy, safety and tolerability in two patient populations, namely those with symptomatic PN (Stratum I)[11] and non-symptomatic PN (Stratum II).[61] Among the other four studies, there was some variation in the description of the baseline impact of PN. One case series and the individual case report described children with symptomatic PN,[55, 63] the ongoing interventional study enrolled patients with significant morbidity[62] and another case series recruited participants with significant or potentially significant morbidity.[56] The eighth study was a single-arm trial recruiting adults with NF1, inoperable PN and at least one PN-related morbidity.[59]

Although eight eligible studies were identified for the SLR, the main source of data was one study, namely Stratum I of Phase II of the SPRINT study.[11] Since the exclusion of the other seven studies was not explained in the CS,[1] the ERG requested further information in the clarification letter (questions A8 and A15).[57] In the reply to question A8, the company stated that all studies listed in Table C3 of the CS were relevant for inclusion. However, as part of the reply to question A15, the company tabulated reasons for excluding the seven studies in question.[53] The company's rationale for exclusion is presented in Table 4.4 along with the ERG's assessment of study eligibility. Full data extractions of the identified studies can be found in Appendix 2 of the CS.[1]

The methodology of SPRINT Phase II Stratum I is presented in Table 4.5 and the baseline characteristics are reported in Table 4.6.

Table 4.4: Company versus ERG assessment of relevance of identified studies to the decision problem

Study reference	Company's assessment of relevance to DP	ERG's assessment of relevance to DP*
Baldo et al. 2020[55]	Not considered relevant due to presenting results of a small case series (N=9), with unclear robustness/precision of the reported results (see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).[1]	The population and intervention are relevant. The only relevant outcome is AEs. The outcome of change in volume of PN is not reported using the definitions of partial/complete response as specified in the CS. The company's basis for non-relevance (small sample size and imprecision) is not an exclusion criterion for the SLR. This study should be included for the data on AEs.
Dombi et al. 2016[60]	Not considered relevant to the DP due to presenting the results of a dose-escalation phase 1 study (SPRINT Phase I).	Agree with company's assessment.
Espirito Santo et al. 2020[56]	Not considered relevant due to presenting only categorical results of a small case series (N=19; see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).[1]	The population and intervention are relevant. Reported (for subgroups) frequencies of improvement in pain, disfigurement, physical functioning (motor function in the study) and urinary incontinence. Reported AEs. Tabulated patient-level data on duration of selumetinib treatment (months). The company's basis for non-relevance (small sample size and categorical data) is not an exclusion criterion for the SLR. Some data are not categorical (e.g., duration of treatment). This study should be included for the data on AEs.
Glassberg et al. 2020[61]	Not considered relevant due to presenting results of Stratum II of the SPRINT Phase II study, which falls outside of the licensed indication of selumetinib (by including patients with NF1 PN *which have the potential to become symptomatic*).	Agree with company's assessment. The focus is an asymptomatic population which falls outside of the NICE final scope.[54]
Gross et al. 2020[11]	Considered to be relevant to the DP by presenting results of SPRINT Phase II Stratum I, which also supported the marketing authorisation for selumetinib in the relevant indication.	Agree with company's assessment.
Kudek et al. 2019[62]	Not considered relevant due to presenting only limited results of an ongoing small case study (N=3; see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).[1]	Agree with the company's judgement of non-relevance. This is a conference abstract of an ongoing study. The ERG's assessment is based on Tables 39 to 43 (inclusive)[#] of the CS.[1] The population is relevant. Two of the three children recruited received

Study reference	Company's assessment of relevance to DP	ERG's assessment of relevance to DP*
		selumetinib and one received trametinib. However, no relevant outcome data were reported.
O'Sullivan Coyne et al. 2020[59]	Not considered relevant due to presenting results for adult (≥18 years of age) patients with NF1 PN only.	Agree with company's assessment. Adult population, therefore outside of the NICE final scope.[54]
Passos et al. 2020[63]	Not considered relevant due to presenting only limited results of a single case study (N=1; see Appendix 17.2 of the submission document for further details on the critical appraisal of this study).[1]	Agree with company's assessment (presentation of limited data).

Based on Table 8 of the company's response to the clarification letter[53]
* The ERG's assessment refers to information within the CS and the NICE final scope.[1, 54]; # Not included in the references submitted by the company. Assessment based on information provided in the CS.
AE = adverse event; CS = company submission; DP = decision problem; ERG = Evidence Review Group; NF1 = type 1 neurofibromatosis; NICE = National Institute for Health and Care Excellence; PN = plexiform neurofibroma; SLR = systematic literature review

Table 4.5: Summary of methodology of SPRINT Phase II Stratum I

Study name	SPRINT Phase II (NCT01362803)
Objective	To evaluate the confirmed partial and complete response rate to selumetinib in paediatric patients with NF1 with inoperable PN
Location	US (four study centres)
Design	Interventional study (open-label, Phase II)
Duration of study	Trial is ongoing
Patient population	Stratum I: Paediatric patients aged 2–18 years with symptomatic, inoperable PN associated with NF1
Sample size	50
Key inclusion criteria[a]	• Aged 2–18 years • BSA ≥0.55 m^2, if able to swallow whole capsules Diagnosis of NF1: • Positive genetic testing for NF1, or • At least one of the NIH consensus diagnostic criteria additional to PN

Study name	SPRINT Phase II (NCT01362803)
	Inoperable, symptomatic PN: • PN were required to be measurable, defined as a lesion of at least 3 cm, measured in one direction • A PN was defined as inoperable if it could not be surgically completely removed without risk of substantial morbidity due to encasement or close proximity to vital structures, invasiveness, or high vascularity • Patients who had previously undergone surgery for a PN were eligible provided the PN was not completely resected and was still measurable • A PN was defined as symptomatic if it caused significant morbidity including (but not limited to) deformity or disfigurement, limb hypertrophy or loss of function, pain, airway, or great vessel compromisation, or nerve compression in the regions of the brachial or lumbar plexus
Key exclusion criteria[a]	• Patients for whom the need for surgical intervention of the target PN was anticipated within the first eight cycles of treatment • Use of any investigational agent within the previous 30 days • Ongoing radiation therapy, chemotherapy or hormonal therapy directed at the tumour, immunotherapy, or biologic therapy • Inability to undergo MRI or contraindication for MRI • Prior treatment with selumetinib or another MEK1/2-specific inhibitor • Evidence of an optic glioma, malignant glioma, MPNST or other cancer requiring treatment with chemotherapy or radiation therapy
Intervention(s) and comparator(s)	**Intervention**: Selumetinib 25 mg/m^2 BSA BID (n=50) **Comparator**: N/A (single arm trial)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Long-term safety follow-up was planned for a duration of seven years from the initiation of treatment, or five years after completion of selumetinib treatment, whichever takes longer. Follow-ups include an annual health check and safety evaluations. Median duration of follow-up as of the most recent DCO (29 March 2019) is 3 years, based on a median number of 36 treatment cycles (each 1 month long). One patient was lost to follow-up.

Study name	SPRINT Phase II (NCT01362803)
Statistical tests	The sample size for the primary objective was based on a target response rate of >15%. With a total of 50 evaluable, symptomatic patients, an exact binomial test with a nominal one-sided 2.5% significance level will have 90% power to detect the difference between a null hypothesis response rate of 15% and an alternative hypothesis response rate of 36%. No formal hypothesis testing was performed. Descriptive statistics include the number of non-missing patients (n), mean, standard deviation, median, minimum, and maximum values for continuous variables, while numbers and percentages of patients are presented for categorical variables. The FAS included all patients who received at least one dose of selumetinib. The FAS was the same as the SAS and the ITT population.
Primary outcomes (including scoring methods and timings of assessments)	• ORR to selumetinib, defined as the rate of confirmed PR and CR (PR defined as PN decrease ≥20% compared to baseline; CR defined as the disappearance of the target PN) using centrally read volumetric MRI A target PN was identified for each patient. The target PN was defined as the clinically relevant PN and was required to be amenable to volumetric MRI assessment. PN volumetric evaluation was scheduled every four cycles for the first 25 cycles, with the first evaluation taking place prior to cycle 5. After cycle 25, evaluations were scheduled every six cycles, and at the end of therapy. For long-term follow-up, evaluations were to occur at six-monthly intervals for two years, then every two years or as clinically indicated.
Secondary outcomes (including scoring methods and timings of assessments)	**Tumour Volumetric Responses:** • BOR to selumetinib • Duration of response to selumetinib • Effect of selumetinib on PN growth rate • TTP and PFS in progressive PN (≥20% increase in PN volume within 12–15 months prior to enrolment) PFS**Error! Reference source not found.**PN volumetric evaluation was scheduled every four cycles for the first 25 cycles, w ith the first evaluation taking place prior to cycle 5. After cycle 25, evaluations were scheduled every six cycles, and at the end of therapy. For long-term follow-up, evaluations were to occur at six-monthly intervals for two years, then every two years or as clinically indicated. The most clinically relevant PN was selected at baseline by the treating physician as the ‘target lesion’ and was used to determine treatment response. Assessment of PN response and progression in the trial was conducted using volumetric analysis MRI, performed centrally by the NCI (non-blinded).

	Clinical Outcome Measures:
	At baseline, all patients were assigned to one or more categories of PN-related morbidity based on the location of their target PN and clinical presentation. This assignment determined the patient- and observer-reported outcomes and the functional evaluations to be completed. HRQoL and pain evaluations were assessed prior to cycles 3, 5, 9 and 13, then after every 12 cycles (prior to cycles 25, 37, etc). These assessments were collected irrespective of patients' baseline PN-associated morbidities. Functional evaluations were assessed prior to cycles 5, 9 and 13, then after ever 12 cycles (prior to cycles 25, 37, etc). These assessments were collected only from patients with those morbidities at baseline.
	
	• **HRQoL**: PedsQL total score and the four domain scores:
	  • Physical functioning
	  • Emotional functioning
	  • Social functioning
	  • School functioning
	• **Pain**: NRS-11, PII, Pain Medication Survey
	• **Motor function**: PROMIS (mobility and upper extremity), strength, range of motion, grooved pegboard test, grip strength and key pinch, leg length evaluation
	• **Airway function**: AHI sleep study, PFTs
	• **Bowel/bladder function**: DVQ
	• **Visual function**: Visual acuity, exophthalmometry
	• **Disfigurement**: Captured via photography
	• **Physical functioning**: 6MWT (only in patients with lower extremity PN, cord compression or airway PN)
	
	The primary analysis of the clinical outcome measures was based on descriptive statistics and MMRM analyses summarising the changes over time. MMRM analyses were used to allow for correlation between observations within a subject.
	Supportive analyses using CMTs were conducted to help with interpretation of clinical benefit. Thresholds for meaningful change were estimated using both distribution (one-half standard deviation) and anchor-based (with the GIC as the anchor) approaches. Whenever available, data from published literature were used to define the CMT. The CMT definitions were as follows:
	Improvement: a change from baseline ≥ CMT points
	Deterioration: a change from baseline ≤ −CMT points

Study name	SPRINT Phase II (NCT01362803)
	No change: a change from baseline between (−CMT to CMT) **Global Impression of Change:** A GIC scale was used to assess change in tumour pain, overall pain and tumour-related morbidities compared to baseline. GIC was assessed at pre-cycles 3, 5, 9 and 13, then every 12 cycles. **Safety Measures:** • Detailed clinical evaluation • Laboratory studies Evaluations were assessed prior to cycles 2 to 5, then every other cycle (prior to cycles 7, 9, 11 and 13), then every four cycles (prior to cycles 17, 21 and 25), then every 6 cycles (prior to cycles 31, 37, 43, etc). • ECG/ECHO or cardiac MRI ECG was assessed as clinically indicated. ECHO was assessed prior to cycles 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to cycles 31, 37, 43, etc). • Ophthalmologic exams Ophthalmological evaluations were assessed prior to cycles 5 and 13, then yearly or more often as clinically indicated. • Symptom checklist • Patient diary • AEs These safety evaluations were assessed prior to cycles 3, 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to cycles 31, 37, 43, etc). **Other Secondary Outcomes:** • Bone mineral density in patients with impaired bone mineral density at the time of enrolment[b] • Day 1 and steady state pharmacokinetics of selumetinib[c] • Changes in the size of the optic pathway tumour or other glioma[d] • Changes in ERK phosphorylation in PBMCs[e]
Based on Table C5 of the CS[1]	

Study name	SPRINT Phase II (NCT01362803)
[a] For full details of the inclusion and exclusion criteria please see AstraZeneca Data on File (SPRINT protocol, SAP).[66] [b] Data on bone mineral density have not been presented within the CS, as the results are not relevant for the scope of this appraisal. [c] Pharmacokinetic analyses are included in the SPRINT CSR, but have not been presented within this evidence submission as these results are not relevant for the scope of this appraisal.[32] [d] This objective was of an exploratory nature for research purposes, and data were not collected in the clinical database.[66] [e] There was insufficient viable data for this objective to be included in the SPRINT CSR.[32] 6MWT = six-minute walk test; AE = adverse event; AHI = apnoea hypopnoea index; BID = twice daily; BOR = best objective response; BSA = body surface area; CMT = clinically meaningful threshold; CR = complete response; CS = company submission: CSR = clinical study report: DCO = data cut-off; DVQ = dysfunctional voiding questionnaire; ECG = electrocardiogram; ECHO = echocardiogram; FAS = full analysis set; GIC = global impression of change; HRQoL = health-related quality of life; ITT = intention-to-treat; MMRM = mixed-effect model repeated measures; MPNST = malignant peripheral nerve sheath tumour; MRI = magnetic resonance imaging; N/A = not applicable; NCI = National Cancer Institute; NF1 = type 1 neurofibromatosis ; NIH = National Institutes of Health; NRS-11 = numerical rating scale 11; ORR = objective response rate; PBMC = peripheral blood mononuclear cells; PedsQL = Pediatric Quality of Life Inventory; PFS = progression-free survival; PFT = pulmonary function test; PII = pain interference index; PR = partial response; PROMIS = Patient-reported Outcomes Information System; SAP = safety analysis plan; SAS = safety analysis set; TTP = time to progression; US = United States (of America)	

Table 4.6: Baseline patient characteristics in SPRINT Phase II Stratum I and external comparator studies

Patient characteristics	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
Age, years median (range)	[redacted]	7.8 (3.0–17.0)	8.2 (3–17.7)
Age, years mean (SD)	[redacted]	NR	NR
Sex, n (%)			
Male	[redacted]	57 (61)	14 (48)
Female	[redacted]	36 (39)	15 (52)
Race, n (%)			
White	[redacted]	72 (77)	NR
Black or African American	[redacted]	7 (8)	NR
Asian	[redacted]	1 (1)	NR
Unknown	[redacted]	13 (14)	NR
Ethnic group, n (%)			
Not Hispanic or Latino	[redacted]	NR	NR
Hispanic or Latino	[redacted]	NR	NR
Unknown	[redacted]	NR	NR
Not reported	[redacted]	NR	NR
Height, cm median (range)	[redacted]	NR	NR
Weight, kg median (range)	[redacted]	NR	NR
BSA, m^2 median (range)	[redacted]	NR	NR
BSA, m^2 mean (SD)	[redacted]	NR	NR

Based on CS,[1] Gross et al. 2020 (DCO 29th March 2019),[11], Widemann et al. 2014,[64] and SPRINT CSR[32]
BSA = body surface area; CS = company submission; NR = not reported; PN = plexiform neurofibroma; SD = standard deviation

ERG comment: Data from two other studies could have been included in the CS. Both provided data on AEs[55, 56] and one potentially provided data on duration of response.[56] Tables 4.7 and 4.8 present details on Baldo 2020 while Tables 4.9 and 4.10 present details on Espirito Santo 2020.

All trials, SPRINT, Baldo et al. 2020, and Espirito Santo et al. 2020 are single-arm trials, i.e. did not include a comparator arm, which limits the robustness of the results.[11, 55, 56]

It should be noted that the SPRINT trial has been conducted in the USA, i.e. no UK patients were included. However, according to the CS, *"based on an assessment of baseline characteristics, patients*

from the SPRINT Phase II clinical trial are broadly representative of the UK paediatric NF1 PN patient population, despite being recruited from US sites, which has been confirmed by clinical experts in the UK".[1]

Table 4.7: Summary of methodology for Baldo 2020

Study name	Baldo 2020
Objective	To describe a prospective case series of patients treated with selumetinib with emphasis on drug AEs
Location	Italy
Design	Interventional case-series (single-arm)
Duration of study	November 2017 to January 2020
Patient population	Paediatric patients with NF1 and inoperable PN
Sample size	9
Key inclusion criteria	Patients with NF1 and inoperable PN Patients who received selumetinib from November 2017 to January 2020
Key exclusion criteria	NR
Intervention(s) and comparator(s)	Intervention: Selumetinib BID; dosage between 20 mg/m^2 and 25 mg/m^2 Comparator: N/A
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were monitored with follow-up visits every 3 months. Direct phone communication was also established with the patient's parents and/or the patient themselves so that they could contact the clinician if they experienced any new AEs. MRI or CT scans were performed to assess the neurofibroma size 3 months after the beginning of treatment, and then every 6 to 9 months. The mean follow-up was 12 months (range 3 to 26 months).
Statistical tests	All data were analysed using descriptive statistics
Outcomes (including scoring methods and timings of assessments)	AEs Phone communication was established with patients/their parents to monitor possible AEs, in addition to a full clinical examination every 3 months comprising: a complete ophthalmological exam, a pneumological visit with a spirometry (if allowed by age and compliance of the patient), a cardiological visit with ECG and ECHO, and blood tests. Tumour size in response to selumetinib MRI or CT scans were performed to assess the variation in size of the PN 3 months after treatment initiation; and then again, every 6 to 9 months. The PN volume measurement and 3D evaluation were performed on axial scans with Horos™ by a radiologist with expertise in NF1 imaging evaluation. Tumour reduction was defined as a mass shrinkage >20% Tumour stabilisation was defined as a mass change between zero and 20% Tumour growth was defined as any expansion of the tumour at the end of the follow-up

Study name	Baldo 2020
Based on Table 10 of the CS[1] and Baldo et al. 2020[55] AE = adverse event; BID = twice daily; CS = company submission; CT = computerised tomography; ECG = electrocardiogram; ECHO = echocardiogram; MRI = magnetic resonance imaging; N/A = not applicable; NF1 = type 1 neurofibromatosis; NR = not reported; PN = plexiform neurofibroma	

Table 4.8: Summary of patient baseline characteristics reported in Baldo 2020

Baseline characteristics	
Number of patients	9
Number of PN	17
Age at start of treatment, years	
Mean	11
Range	4–18
Sex, n (%)	
Male	7 (78)
Female	2 (22)
Localisation of PN, n (%)[a]	
Head/neck	6 (35)
Chest/back	3 (18)
Abdomen/pelvis	3 (18)
Upper limbs	1 (6)
Lower limbs	4 (23)
Based on Table 11 of the CS[1] and Baldo et al. 2020[55] [a] Number and percentage calculated from total number of PN CS = company submission; PN = plexiform neurofibroma	

Table 4.9: Summary of methodology for Espirito Santo 2020

Study name	Espirito Santo 2020
Objective	To describe the experience with selumetinib used in a single institution for the treatment of inoperable PN in NF1
Location	Portugal
Design	Case series
Duration of study	Mean follow-up: 223 days
Patient population	NF1 patients with inoperable PN associated with significant morbidity or potentially significant morbidity, aged 3 to 19 years
Sample size	19
Key inclusion criteria	NF1 PN patients that fulfilled the criteria for selumetinib treatment: Inoperable PN associated with significant or potentially significant morbidity At least 6 months of follow-up MPNST exclusion after FDG-PET/CT scan Normal laboratory results and cardiac function
Key exclusion criteria	Asymptomatic PN MPNST

Study name	Espirito Santo 2020
	Low performance status
Intervention(s) and comparator(s)	Intervention: Selumetinib 25 mg/m^2 BID Comparator: N/A
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). **Duration of follow-up, participants lost to follow-up**	Patients were followed-up monthly (physical examination, evaluation of treatment adherence and blood analysis), every 3 months (ECHO) and 6 months (MRI). Mean length of follow-up was 223 days (35–420 days). The number of patients lost to follow-up is not reported.
Statistical tests	Favourable response/PN shrinkage was defined as at least a 30% decrease in the sum of diameters of target lesions. Descriptive statistics include median, minimum, and maximum values for continuous variables numbers while numbers and percentages of patients are presented for categorical variables.
Primary outcomes (including scoring methods and timings of assessments)[a]	**Clinical improvement** For clinical evaluation, the single most trouble symptom in each patient was considered; a qualitative all or nothing response (visual inspection for disfigurement), and self-reported benefits (any improvement: yes/no, improvement of specific symptoms: yes/no). **PN size** Measured using MRI, a decrease in size was defined as at least a 30% decrease in the sum of diameters of target lesions. The RECIST criteria was used to assess tumour reduction. MRI assessment occurred every 6 months. **Safety** AEs were assessed using the CTCAE criteria. Physical examinations were carried out monthly.

Based on Table 16 of the CS[1] and Espirito Santo et al. 2020[56]
AE = adverse events; BID = twice daily; CS = company submission; CT = computerised tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; MPNST = malignant peripheral nerve sheath tumours; MRI = magnetic resonance imaging; N/A = not applicable; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibroma; RECIST = Response Evaluation in Solid Tumours

Table 4.10: Summary of patient baseline characteristics reported in Espirito Santo 2020

Baseline characteristics	
Number of patients	19
Median age (range) at enrolment, years	13 (3–19)
Male, n	15
Female, n	4
Median PS score (range)	80 (50–90)
Target PN location, n	
Head and neck	6
Chest	5
Pelvis	5

Baseline characteristics	
Upper and lower limbs	3
Progression status of target PN at enrolment, n	
Progressive	8
Nonprogressive	11
Most important complication related to PN at baseline, n	
Disfigurement	8
Pain	5
Motor dysfunction	3
Urinary symptoms	4

Based on Table 11 of the CS[1] and Espirito Santo et al. 2020[56]
[a] Number and percentage calculated from total number of PN
CS = company submission; PN = plexiform neurofibroma; PS = performance status

4.2.2 Details of relevant studies not included in the submission

As detailed in Section 4.2.1, the ERG assessed the references identified by the SLR and considers two additional studies to be relevant for this submission.[55, 56]

4.2.3 Summary and critique of company's analysis of validity assessment

In alignment with the ERG's assessment of the eight included studies in the SLR (see Table 4.4), having identified Baldo et al. 2020[55] and Espirito Santo et al. 2020[56] as relevant to DP in addition to Gross et al. 2020,[11] the ERG included the critical appraisals of these three studies, using the NICE adapted version of the Critical Appraisal Skills Programme (CASP) tool in this section.[67]

As stated in Section 4.1.4 of this report, the process of quality assessment used by the company is not in line with best practice, e.g. the Cochrane Handbook states that at least two people should work independently on the risk of bias assessment as *"duplicating the risk-of-bias assessment reduces both the risk of making mistakes and the possibility that assessments are influenced by a single person's biases"*.[58] Thus, the ERG re-assessed the three included studies using the same quality criteria, and results are shown in Table 4.10.

ERG comment: In question 1 (recruitment of cohort), the ERG's response differed from the company as the inclusion criteria for patient recruitment is unclear in Espirito Santo et al. 2020[56]. In questions 4 and 5 (regarding confounding factors) where the ERG's response has differed from the company, the ERG did not agree with the justification of N/A (not applicable) in confounding due to being a single arm study for Baldo et al. 2020 and Espirito Santo et al. 2020. The study authors have neither clearly identified or considered potential confounders in their study designs or outcome measurements. The ERG considers these three observational studies to be of low quality.

Table 4.11: Critical appraisal of included studies

Study question	Espirito Santo 2020[56]		Baldo 2020[55]		SPRINT Phase II Stratum I[11]	
	CS	ERG	CS	ERG	CS	ERG
1. Was the cohort recruited in an acceptable way?	Yes	Not clear	Not clear	Not clear	Yes	Yes
2. Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes
4. Have the authors identified all important confounding factors?	N/A	No	N/A	No	Yes	No
5. Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	No	N/A	No	Not clear	No
6. Was the follow-up of patients complete?	Yes	Yes	Yes	Yes	No	No
7. How precise (for example, in terms of confidence interval and p values) are the results?	N/A	N/A	Not clear	N/A	Not clear	Yes

Based on Table C15 (p.93), 15 (p.264), and 21 (p.268) of the CS[1], Espirito Santo 2020[56], Baldo 2020[55], Gross 2020[11]
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study[67]
CS = company submission; CASP = Critical Appraisal Skills Programme; ERG = Evidence Review Group; N/A = not applicable

4.2.4 Summary and critique of results

This Section provides a summary and critique of the results presented in the CS. Section 4.2.4.1 presents outcomes related to efficacy, Section 4.2.4.2 those related to AEs while Section 4.2.4.3 discusses the results of the propensity score analysis.

4.2.4.1 Efficacy

4.2.4.1.1 Complete and partial response rate

The CS presented data on the objective response rate (ORR), the primary outcome, and the best objective response (BOR) for SPRINT Phase II Stratum I compared with the National Cancer Institute (NCI) Natural History study and the placebo arm of the tipifarnib study (summarised in Table 4.12 below).[1] Among these outcomes, comparator data were only available from the Natural History study for ORR.

- ORR was defined as the percentage of participants with complete response (CR, disappearance of the target PN) or confirmed partial response (cPR) assessed with volumetric MRI analysis.
- BOR is defined as the best response recorded from the start of treatment until progression or the last evaluable volumetric MRI assessment in the absence of progression.
- A partial response (PR) was defined as a decrease in the volume of the target PN by at least 20% relative to baseline.
- A cPR was defined as a PR observed on consecutive restaging examinations at least three months apart.

The results suggested that more participants receiving selumetinib experienced a reduction in PN volume of at least 20% when compared with usual care (68% vs. 0% for Phase II Stratum I of SPRINT versus Natural History study respectively). The follow-up period was 3 years.[1]

Table 4.12 also provides details of the outcome of BOR for which no comparator data were available. Ninety percent (45/50) of patients treated with selumetinib in the SPRINT study Phase II Stratum I had a BOR of reduction in PN volume from baseline, and 74% (37/50) of patients experienced at least 20% reduction in PN volume at BOR (confirmed or unconfirmed PR). In 70% (35/50) of these patients, the reduction in target PN volume from baseline of 20% or more was confirmed on consecutive examinations at least 3 months apart. No patients had a BOR of disease progression. The median change in PN volume at best response was -27.9% (range -55.1 to 2.2).[1, 11] Figure 4.2 presents a waterfall plot showing the best volumetric response for each target PN and the cycle during which this best response was achieved.

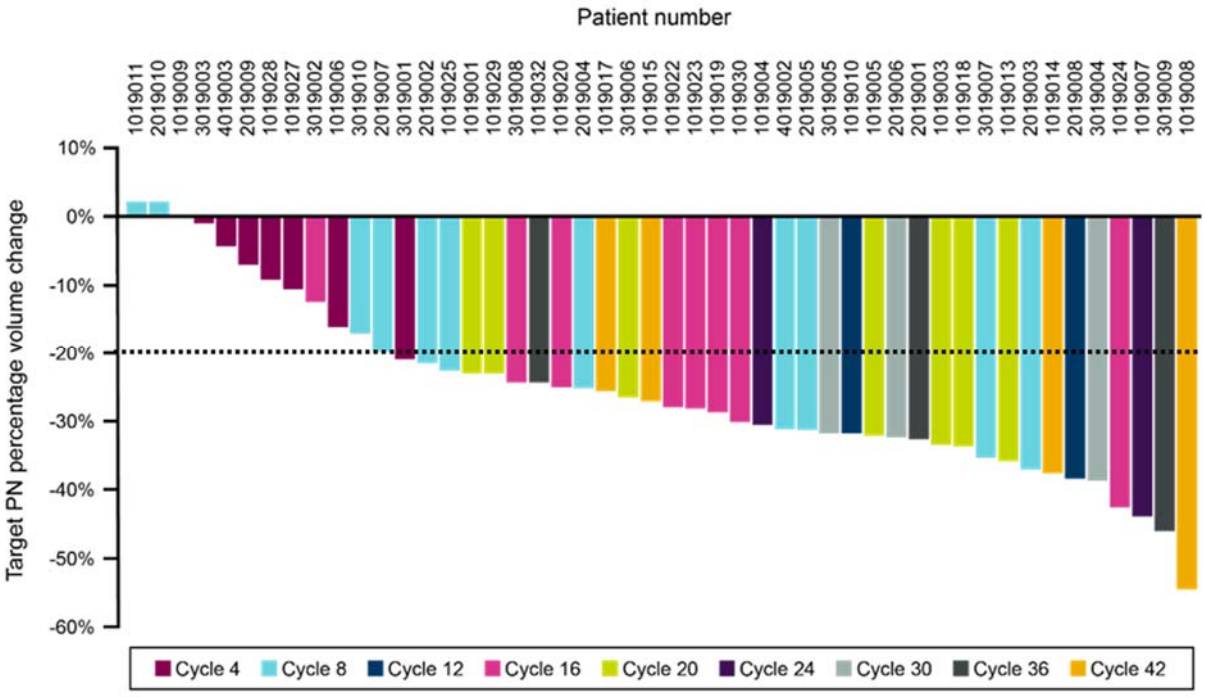
Table 4.12: Summary of ORR and BOR for PN volumetric results

Tumour volumetric outcome measure	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
Primary outcome			
ORR (%)	68[a]	0	N/A
Secondary outcomes			
BOR			
BOR of reduction in PN volume from baseline (%)	90	N/A	N/A

Tumour volumetric outcome measure	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
≥20% reduction in PN volume at BOR (%)	74	N/A	N/A
Duration of response	8 cycles	N/A	N/A

Based on Table C16 of the CS[1] which was in turn based on Gross et al. 2020,[11] Widemann et al. 2014,[64] and the SPRINT CSR.[32]
[a] The accompanying text in the CS confirmed that this percentage referred to 34/50 children with a cPR.[1] This was confirmed in the company's response to the clarification letter (question A17). In their response, the company also stated that a further three patients (6%) experienced an unconfirmed PR. Therefore, a total of 37/50 patients experienced a PR (74%, 95% CI 60 to 85). No patients experienced a CR.[53]
BOR = best objective response; cPR = confirmed partial response; CR = complete response; CS = company submission; N/A = not applicable; ORR = objective response rate; PN = plexiform neurofibromas; PR = partial response;

Figure 4.2: Best volumetric response from baseline in target PN volume in SPRINT Phase II Stratum I



Based on Figure C3 of the CS[1] which in turn in based on Gross et al., (2020)[11]
The cut-off for PR, a ≥20% reduction in PN volume, would be indicated with a line drawn horizontally at the -20% point.[1]
CS = company submission; PN = plexiform neurofibroma; PR = partial response

4.2.4.1.2 Growth rate of PN

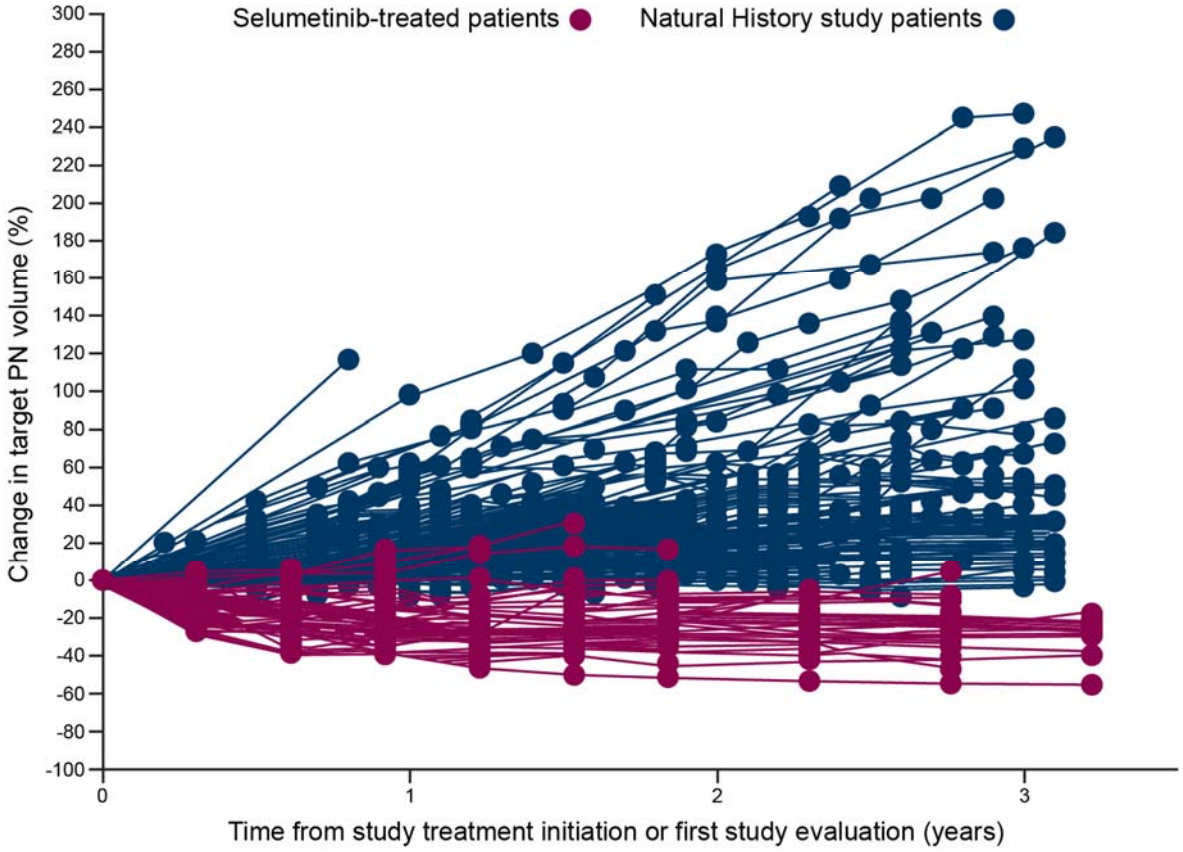
Comparator data were available from the Natural History study. None of the participants receiving selumetinib displayed a PN growth rate of 20% or more per year (range -27.0% to 19.8% per year), compared with 43% of patients in the age-matched cohort of the Natural History study. The median change in PN volume in selumetinib-treated participants was a 23% decrease compared to a 77% increase observed in the Natural History study. The follow-up period was 3 years.[1] The data are summarised in Table 4.13 and Figure 4.3 below.

Table 4.13: Naïve comparison of SPRINT Phase II Stratum I to the Natural History study age-matched cohort for PN growth rate

Tumour volumetric outcome measure	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
Patients with a PN growth rate >20% per year, % (n)	0 (0)[a]	43 (40)	N/A
Median change in PN volume, between baseline and most recent MRI, % (range)	-23 (-55.1 – +30)	+77 (-40 – +1429)	N/A

Based on Tables C16 and C17 of the CS[1] which was in turn based on Gross et al. 2020[11]
[a] The range of reported values for PN growth per year were -27.0% to 19.8%.[1]
CS = company submission; MRI = magnetic resonance imaging; PN = plexiform neurofibroma

Figure 4.3: Percentage change in target PN volume during selumetinib treatment in SPRINT Phase II Stratum I compared to an age-matched Natural History study control cohort



Based on Figure C4 of the CS[1] which was in turn based on Gross et al. 2020[11]
CS = company submission; PN = plexiform neurofibroma

4.2.4.1.3 Disfigurement

No formally planned method for assessing the changes in disfigurement from baseline were reported, however, subjective improvements in the appearance of disfigurements (as could be seen in Figure C15, page 114 of the CS) following selumetinib treatment were reported.[1]

ERG comment: As there were no parameters for judging the improvements of PN disfigurements, the ERG cannot assert the validity of the company's statement on the positive effects of selumetinib on disfigurements.

4.2.4.1.4 Physical functioning

Physical functioning and physical activity were assessed using PROMIS (Patient Reported Outcomes Measurement Information System) mobility and upper extremity scales (see Table 4.14 for change from baseline scores).[1] The CS reported a trend towards [redacted].[1] Between baseline and pre-cycle 13, [redacted].[1] In the mixed-effect model repeated measure (MMRM) analysis of the strength of manual muscle testing (MMT) [redacted].[1] An [redacted] was also observed.[1] MMRM analysis of range of motion in patients with a target PN in any body quadrant also [redacted].[1] A trend [redacted] was also seen.[1]

ERG comment: In Figure 19 of the SPRINT clinical study report (CSR),[32] "[redacted]" can only been seen in parent-reported PROMIS mobility scores while [redacted] Regarding PROMIS upper extremity change from baseline assessments, although [redacted] (as seen in Figure 20 of the SPRINT CSR[32]), there was also [redacted] that could bring into question any conclusion concerning the effects of selumetinib on upper extremity physical function.

Table 4.14: Functional and PRO assessments of PN-associated morbidities in SPRINT Phase II Stratum I

PRO instrument/ functional evaluation	Key items/tests	Eligible for assessment at baseline	Pre-Cycle 13 change from baseline assessment (MMRM analysis*)	Pre-Cycle 25 change from baseline assessment (MMRM analysis*)	Overall results
Disfigurement					
Photographs	NR	[redacted] with disfigurement	NR	NR	There was no formally planned method for assessing changes in disfigurement. Many patients and parents reported subjective improvement in appearance
Motor function					
PROMIS® mobility	[redacted]	[redacted]	Self-report: [redacted] Adjusted mean (95% CI): [redacted] Parent-report: [redacted] Adjusted mean (95% CI): [redacted]	Self-report: [redacted] Adjusted mean (95% CI): [redacted] Parent-report: [redacted] Adjusted mean (95% CI): [redacted]*	[redacted]
PROMIS® upper extremity	[redacted]	[redacted]	Self-report: [redacted] Adjusted mean (95% CI): [redacted]	Self-report: [redacted] Adjusted mean (95% CI): [redacted] Parent-report: [redacted] Adjusted mean (95% CI): [redacted]	[redacted]

PRO instrument/ functional evaluation	Key items/tests	Eligible for assessment at baseline	Pre-Cycle 13 change from baseline assessment (MMRM analysis*)	Pre-Cycle 25 change from baseline assessment (MMRM analysis*)	Overall results
			Parent-report: [redacted] Adjusted mean (95% CI): [redacted]	[redacted]	
Strength (manual muscle test)	[redacted]	[redacted]	[redacted] Adjusted mean (95% CI): [redacted]	[redacted] Adjusted mean (95% CI): [redacted] [redacted]	[redacted]
Range of motion	[redacted]	[redacted]	[redacted] Adjusted mean (95% CI): [redacted]	[redacted] Adjusted mean (95% CI): [redacted] [redacted]	[redacted]
Grooved pegboard	[redacted]	[redacted]	[redacted]	Patients with unilateral upper body PN: [redacted] Patients with bilateral upper body PN: [redacted]	Patients with unilateral upper body PN [redacted] Patients with PN affecting both upper body quadrants [redacted]
Grip strength and key pinch	[redacted]	[redacted]	[redacted]	[redacted]	Grip strength showed [redacted]

PRO instrument/ functional evaluation	Key items/tests	Eligible for assessment at baseline	Pre-Cycle 13 change from baseline assessment (MMRM analysis*)	Pre-Cycle 25 change from baseline assessment (MMRM analysis*)	Overall results
					Key pinch
Leg length disparity					
Visual function					
Visual acuity			(patients with enucleation of the affected eye or vision limited to light perception and position or worse were excluded from this evaluation)	NR	
Amount of exophthalmos				NR	
Airway function					
AHI (sleep study)					

PRO instrument/ functional evaluation	Key items/tests	Eligible for assessment at baseline	Pre-Cycle 13 change from baseline assessment (MMRM analysis*)	Pre-Cycle 25 change from baseline assessment (MMRM analysis*)	Overall results
$FEV_1/FEV_{0.75}$ (L)	[redacted]	[redacted]	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted]
R_5	[redacted]	[redacted]	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	NR	[redacted]
R_{20}	[redacted]	[redacted]	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted] ([redacted] patients with a tracheostomy were excluded from this evaluation)	[redacted]
Bowel/ bladder function					
DVQ	[redacted]	[redacted]	Self-report: NR Parent-report: [redacted]	Self-report: NR Parent-report: [redacted]	[redacted] however, the CIs were wide. Due to insufficient data at baseline ([redacted]), it was not possible

PRO instrument/ functional evaluation	Key items/tests	Eligible for assessment at baseline	Pre-Cycle 13 change from baseline assessment (MMRM analysis*)	Pre-Cycle 25 change from baseline assessment (MMRM analysis*)	Overall results
					to evaluate mean change for self-report scores
Pain					
NRS-11	[redacted]	[redacted]	Physician-selected target tumour pain: [redacted] Adjusted mean (95% CI): [redacted]	Physician-selected target tumour pain: [redacted] Adjusted mean (95% Cl): [redacted]	Reduction in PN-related pain intensity for self-selected pain, target PN pain, overall PN pain and other pain, [redacted]
PII	[redacted]	[redacted]	Self-report: [redacted] Adjusted mean (95% CI): [redacted] Parent-report: [redacted] Adjusted mean (95% CI): [redacted]	Self-report: [redacted] Adjusted mean [redacted] Parent-report: [redacted] Adjusted mean [redacted]	Overall improvement from baseline in self-reported and parent-reported PII scores [redacted] demonstrating that selumetinib reduces pain interference
HRQoL					
PedsQL	[redacted]	[redacted]	Self-report: [redacted]	Self-report: [redacted]	[redacted]

PRO instrument/ functional evaluation	Key items/tests	Eligible for assessment at baseline	Pre-Cycle 13 change from baseline assessment (MMRM analysis*)	Pre-Cycle 25 change from baseline assessment (MMRM analysis*)	Overall results
	[redacted]	[redacted]	Adjusted mean (95% CI): [redacted] Parent-report: [redacted] Adjusted mean (95% CI): [redacted]	Adjusted mean (95% CI): [redacted] Parent-report: [redacted] Adjusted mean (95% CI): [redacted]	[redacted] indicating that selumetinib results in sustained improvements in patient HRQoL
Other					
6MWT	[redacted]	[redacted]	[redacted] Adjusted mean (95% CI): [redacted]	[redacted] Adjusted mean (95% CI): [redacted]	[redacted]

Source: Table C19 of the CS[1] and Tables 32, 33, 34, 37, 39, 40, 48, 49 and 51 of the SPRINT CSR[32]

Assessments for pain was completed irrespective of patients' baseline PN-associated morbidities. All other assessments were collected only from patients with those morbidities at baseline. Not all eligible patients completed each assessment.

* The MMRM analysis permits testing treatment effects at specific timepoints, which is more powerful than a two-sample t-test and can take account of missing data in an unbiased fashion.

6MWT = six-minute walk test; AHI = apnoea-hypopnoea index; CI = confidence interval; CS = company submission; CSR = clinical study report; DVQ = dysfunctional voiding questionnaire; FEV0.75 = forced expiratory volume after 0.75 seconds; FEV1 = forced expiratory volume after 1 second; HRQoL = health-related quality of life; MMRM = mixed-effect model repeated measures; NR = not reported; NRS-11 = numerical rating scale 11; PedsQL = Pediatric Quality of Life Inventory; PII = pain interference index; PN = plexiform neurofibroma; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System

4.2.4.1.5 Visual function

Baseline and pre-cycle 13 (following 12 months of selumetinib treatment) assessments were reported in [redacted] for visual acuity while [redacted] were measured with exophthalmometry at pre-cycle 13.[1] Although the mean visual acuity trended [redacted], these changes could have been due to there being a small sample of patients and variability in patient ages.[1] There was wide variability in amount of exophthalmos results at pre-cycle 13 with [redacted].[1] Overall, there were no statistically significant changes from baseline to pre-cycle 13 in visual function.

4.2.4.1.6 Airway functioning

At pre-cycle 13, [redacted] patients showed improvement in forced expiratory volume after 1 second (FEV_1), [redacted], and [redacted] showed no change in FEV_1.[32] Although [redacted].[1]

ERG comment: R_5 is not included in the SPRINT CSR as an assessment for airway function.

4.2.4.1.7 Bowel and bladder continence

Although there was a [redacted] (as seen in Figure 28 of the SPRINT CSR[32]), wide confidence intervals (CIs) due to a small sample means that no reliable conclusions can be drawn about the effect of selumetinib on bowl and bladder continence. Due to insufficient baseline data([redacted]), mean change in self-reported DVQ scores could not be assessed.[1]

4.2.4.1.8 Pain

The change from baseline results for physician-selected target tumour pain on the numeric rating scale 11 (NRS-11) was the most clinically relevant item in this section as *"it assessed the pain intensity caused by the target PN-related morbidity"*.[32] [redacted] patients completed NRS-11 assessments for physician-selected target PN pain at baseline and at the pre-cycle 13 visit. At baseline, the median score for target PN pain intensity was [redacted], compared to [redacted], demonstrating a [redacted].[1] At pre-cycle 13, [redacted], considered a clinically meaningful improvement. Of these [redacted].[1] [redacted].[1] In the MMRM analysis of PN pain intensity, a [redacted] was seen at pre-cycle 13 and [redacted] (see Table 4.14 for adjusted mean change from baseline scores).[1]

MMRM analysis of the association between post-baseline longitudinal changes in NRS-11 and changes in PN volumes suggested [redacted].[1]

Assessments of pain interference with daily functioning showed overall improvements in both patient- and parent-reported pain interference index (PII) from baseline, [redacted]. There was also [redacted] with self-reported PII.[1] [redacted] showed a clinically meaningful improvement at pre-Cycle 13 while one (3%) patient showed deterioration.[1] Of the [redacted] with parent-reported PII, [redacted] showed a clinically meaningful improvement while [redacted] at pre-cycle 13.[1] There was a [redacted].[1]

ERG comment: Whilst the company's statement that, *"results of the NRS-11 and PII demonstrate the capacity of selumetinib to have a positive, clinically meaningful impact on PN-associated pain,* [redacted]*"*[1] is true for a good number of patients following 12 months of selumetinib treatment, there were still some patients experiencing deterioration or no change in pain intensity or interference with daily functioning.

4.2.4.1.9 HRQoL (children)

Overall, a trend of improvement in self- and parent-reported HRQoL scores was seen over each measurement cycle, based on mean change from baseline in both PedsQL total score and domain scores.[1] The MMRM analysis of change from baseline in PedsQL total score can be seen in Table 4.14. Mean total scores increased from baseline across treatment cycles for both self- and parent-reported scores; these increases were statistically significant at a level of P=0.05, supporting conclusions of the significant benefits of selumetinib for patient HRQoL.[1]

Based on self-reported PedsQL total scores, [redacted] patients had impaired HRQoL at baseline.[1] At pre-cycle 13, [redacted] had impaired HRQoL, and [redacted] of patients showed a clinically meaningful improvement in HRQoL above the clinically meaningful threshold (CMT, see Table 4.15).[1] These results were maintained through to pre-Cycle 25, where only [redacted] had impaired HRQoL, and [redacted] of patients showed a clinically meaningful improvement in HRQoL above the CMT.[1]

Based on parent-reported PedsQL total scores, [redacted] patients had impaired HRQoL at baseline.[1] At pre-cycle 13, [redacted] with parent-reported scores had impaired HRQoL, and [redacted] patients showed an improvement in HRQoL based on the CMT.[1] These results were maintained through to pre-cycle 25, where only [redacted] had impaired HRQoL and [redacted] patients showed a clinically meaningful improvement in HRQoL above the CMT.[1]

ERG comment: In its request for clarification, the ERG asked the company to provide the thresholds for clinically meaningful differences for HRQoL (PedsQL), PN-associated pain, airway function (R5), and motor function (the patient-related mobility and the upper extremity scores).[57] The company in its response provided a table with the respective thresholds, see Table 4.15.[53]

Table 4.15: Clinically meaningful thresholds (CMT) for selected outcome assessments in SPRINT Phase II Stratum I

Clinical outcome assessment	Clinically meaningful threshold (primary analysis)	Supporting reference

HRQoL (PedsQL total score)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores.[a] • Self-reported: [redacted] • Parent-reported: [redacted]	AstraZeneca Data on File (SRINT CSR)[32]
PN-associated pain (NRS-11)	A decrease of two points on the NRS-11 was considered clinically meaningful based on several studies in other populations.	AstraZeneca Data on File (SPRINT SAP)[66] Farrar et al. 2000[68] Kendrick et al. 2005[69] Salaffi et al. 2004[70] Voepel-Lewis et al. 2011[71]
PN-associated pain (PII)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores. • Self-reported: [redacted] • Parent-reported: [redacted]	AstraZeneca Data on File (SRINT CSR)[32]
Motor function (PROMIS mobility)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores. • Self-reported: [redacted] (raw score); [redacted] (transformed) • Parent-reported: [redacted] (raw score); [redacted] (transformed)	AstraZeneca Data on File (SRINT CSR)[32]
Motor function (PROMIS upper extremity)	Using a distribution-based approach, threshold values were based on the half value of the standard deviation of the study baseline scores. • Self-reported: [redacted] (raw score); [redacted] (transformed) • Parent-reported: [redacted] (raw score); [redacted] (transformed)	AstraZeneca Data on File (SRINT CSR)[32]
Airway function (R_5)	Any change of ≥20% from baseline was considered clinically meaningful, with a decrease in resistance indicating improvement and an increase in resistance indicating worsening.[b] Otherwise, it was concluded that no change had occurred. These response criteria are recommended by the REiNS functional group.	AstraZeneca Data on File (SPRINT SAP)[66] Plotkin et al. 2016[29]

Based on Table 9 of response to request for clarification[53]

[a] In addition to the use of distribution-based clinically meaningful thresholds for the primary assessment of HRQoL, patients were also classified with impaired global HRQoL (Yes/No) at each pre-cycle visit, using linearly transformed PedsQL scores; patients were classified with impaired global HRQoL if their total or domain scores fell one standard deviation below the population sample mean as reported by Varni et al 2003[72]

[b] No patients enrolled in this study had a baseline score on the Apnoea-Hypopnoea Index (AHI) of >5, considered to be the lower limit necessary to see a meaningful effect of treatment.

AHI = apnoea hypopnoea index; CMT = clinically meaningful threshold; CSR = clinical study report; HRQoL = health-related quality of life; NRS-11 = Numerical Rating Scale 11; PedsQL = Pediatric Quality of Life Inventory; PII = Pain Interference Index; PN = plexiform neurofibroma; PROMIS = Patient-Reported

Outcomes Measurement Information System; REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis; SAP = statistical analysis plan

4.2.4.1.10 Progression-free survival (PFS)

The median PFS was not reached in SPRINT Phase II Stratum I at the data cut-off on 29 March 2019, see Table 4.16. The Kaplan-Meier curves suggested a continued divergence in PFS between patients receiving selumetinib in SPRINT Phase II Stratum I and those in the Natural History Study age-matched cohort, over the duration follow-up period (presented in Figure 4.4). At 3 years, 84% of patients in SPRINT Phase II Stratum I remained progression-free compared with 15% in the Natural History age-matched cohort.[1, 11]

An additional naïve comparison was conducted by the company to compare the results of the SPRINT Phase II Stratum I clinical study report and external control data from the placebo arm of the tipifarnib Phase II Study 01-C-0222.[32, 64] Since only patients with progressive PN were enrolled in Study 01-C-0222, only patients from SPRINT Phase II Stratum I with progressive PN were used for the comparison.[11]

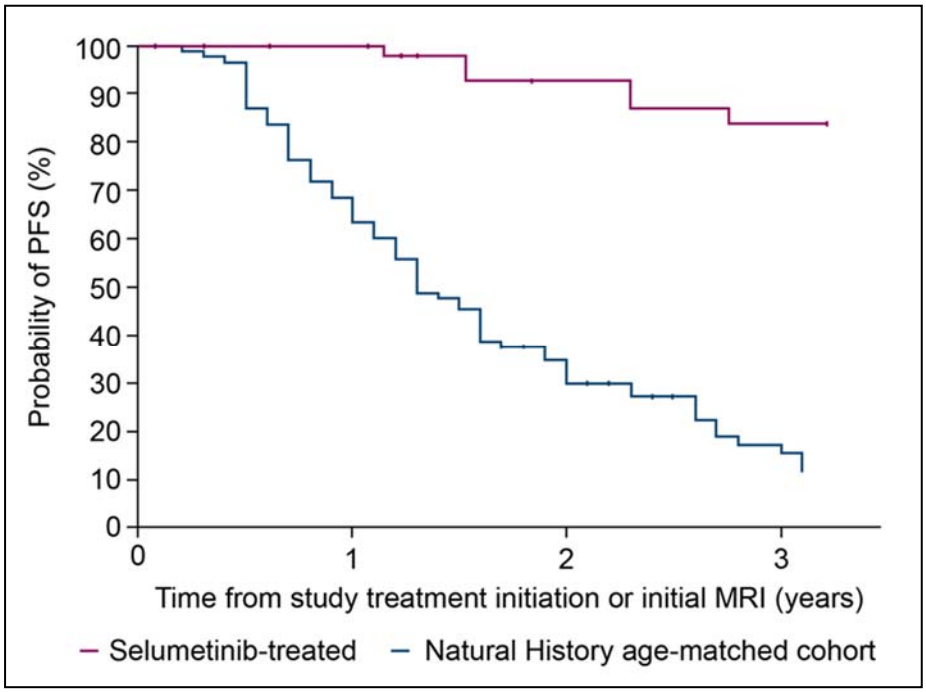
As ORR was not assessed in the tipifarnib placebo arm, the secondary endpoint from SPRINT, PFS, was assessed in this comparison, see Table 4.16. Based on the data cut-off on 29 June 2018, of the patients included in SPRINT Phase II Stratum I, [redacted] patients had progressive PN in the 18 months prior to enrolment. Figure 4.5 suggests that the probability of remaining without progression at 2 years was reported to be 21% (95% CI 7.7 to 37.8) for patients receiving placebo in the tipifarnib trial, compared with [redacted] for the subgroup of patients with progressive PN at enrolment receiving selumetinib in SPRINT Phase II Stratum I.[32]

Table 4.16: Naïve comparison of SPRINT Phase II Stratum I to the Natural History study age-matched cohort for PFS

Tumour volumetric outcome measure	SPRINT Phase II Stratum I (N=50)	Natural History study age-matched cohort (NCT00924196) (N=93)	Placebo arm of the tipifarnib Study 01-C-0222 (NCT00021541) (N=29)
PFS (over 3.2 years of follow-up)			
Median PFS, years (95% CI)	Not reached[a]	1.3 (1.1–1.6)	N/A
Probability of PFS at 3 years, %	84	15	N/A
Probability of PFS at 2 years, %	[redacted]	N/A	21[c]

Based on Tables C16 and C18 of the CS[1] which was in turn based on Gross et al. 2020[11]
[a] The median PFS has not yet been reached, with 12% of patients experiencing disease progression (6/50). [b] To allow for comparison to the placebo arm of the tipifarnib study, these values are based on [redacted] patients with progressive PN in the 18 months prior to enrolment of SPRINT Phase II Stratum I. The text of the CS (page 99) reported this estimate as: [redacted]. [c] The text of the CS (page 99) reported this estimate as: 21% (95% CI 7.7 to 37.8)[1]
CI = confidence interval; CS = company submission; N/A = not applicable; PFS = progression free survival; PN = plexiform neurofibroma

Figure 4.4: PFS during selumetinib treatment in SPRINT Phase II Stratum I compared to the age-matched Natural History study control cohort



Based on Figure C4 of the CS[1] which in turn was based on Gross et al. 2020[11]
CS = company submission; MRI = magnetic resonance imaging; PFS = progression free survival

Figure 4.5: PFS during selumetinib treatment in SPRINT Phase II, Stratum I versus placebo arm of tipifarnib Study 01-C-0222 (patients with progressive PN only)

[redacted]

Based on Figure C5 of the CS[1] which in turn was based on the SPRINT CSR[32]
Footnote from Figure C5 of the CS: DCO for SPRINT data: 29th June 2018. Includes patients with progressive disease in the 18 months prior to enrolment from SPRINT Phase II Stratum I, as all patients in the tipifarnib Study 01-C-0222 had progressive disease. PFS was defined as the time from study treatment/placebo initiation until the pre-cycle/date of objective progression or death (by any cause in the absence of progression) for SPRINT Phase II Stratum I /placebo arm of tipifarnib Study 01-C-0222, respectively. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable volumetric MRI assessment known to be non-progression.[1]
CS = company submission; CSR = clinical study report; DCO = data cut-off; MRI = magnetic resonance imaging; NA = not applicable; PFS = progression-free survival; PN = plexiform neurofibroma

ERG comment: The ERG asked for clarification regarding the use of PFS which could be seen as a surrogate endpoint and which has not been listed as an outcome of interest in the NICE final scope.[57]

In response, the company stated that *"PFS is an important measure of treatment effectiveness due to the impact of progression on PN-associated morbidities and patient HRQoL (…) PFS acts as a measure of the proportion of patients who are experiencing PN volume reduction, and also those who are experiencing PN tumour control/volume stabilisation. In this setting of paediatric patients with NF1 and symptomatic, inoperable PNs, control of, or stopping, PN growth can provide a significant clinical benefit, with patients avoiding the worsening of symptoms, psychological burden and uncertainty which can result from progression.*[REF 17 in response to the request for clarification]. *The PFS endpoint therefore acts as longitudinal measure of both disease stabilisation and tumour volume reduction, encapsulating all relevant treatment effects for patients with NF1 PN (…) PFS was therefore used in the propensity score analysis as it presents a longitudinal view of the efficacy of selumetinib"*.[53]

4.2.4.1.11 Other outcomes

The outcomes of global impression of change and time to progression did not feature in the NICE final scope[54] but were listed as part of the company's consideration of the DP. Details of these outcomes can be found in the CS.[1] Furthermore, PFS (see Section 4.2.4.1.10) and duration of response were reported as well, although not listed in the NICE final scope, see Section 3.3.4.

In terms of the duration of response, the median time to initial response in SPRINT Phase II Stratum I was 8 cycles (range 4 to 20), and the median time to best response was 16 cycles (range 4 to 36). Of the 35 patients who had confirmed PR to selumetinib, 28 (80%) had a durable response to selumetinib treatment, defined as a response lasting for more than 1 year.[1, 11]

4.2.4.2 Adverse events associated with selumetinib

This section summarises the outcome data on AEs for SPRINT Phase II Stratum I,[11] Baldo et al. 2020[55] and Espirito Santo et al. 2020.[56]

4.2.4.2.1 Adverse events associated with selumetinib reported in SPRINT Phase II Stratum I

The company reported a series of summaries of treatment exposure, safety and tolerability results from the 90 day safety update (29 March 2019 data cut off).[73] Additional details of AEs that occurred during the period of the first DCO (29 June 2018) are also included, as reported in the CSR.[32]

At the 90 day safety update, [redacted] were receiving selumetinib treatment.[1, 73] The duration of exposure to selumetinib is summarised in Table 4.17.

Table 4.17: Exposure to selumetinib for SPRINT Phase II Stratum I

Treatment duration	Selumetinib (N=50)
Total treatment duration, days[a]	
Mean (SD)	[redacted]
Median (min–max)	[redacted]
Total treatment years	[redacted]
Total treatment duration[b]	
<12 months, n (%)	[redacted]
≥12 to ≤24 months, n (%)	[redacted]

Treatment duration	Selumetinib (N=50)
>24 to ≤36 months, n (%)	[redacted]
>36 to ≤48 months, n (%)	[redacted]
>48 months, n (%)	[redacted]
Actual treatment duration, (days)[c]	
Mean (SD)	[redacted]
Median (min–max)	[redacted]
Total treatment years	[redacted]

Based on Table C22 of the CS[1] which in turn is based on the 90 day safety update.[73]
[a] Total treatment duration = (last dose date – first dose date + 1). For re-treatment patients, this excludes the off-treatment period between treatment discontinuation and re-treatment. [b] One month = 30.4375 days. [c] Actual treatment duration = sum of days of study dose administered.
CS = company submission; SD = standard deviation

An overall summary of AEs for SPRINT Phase II Stratum I is presented in Table 4.18.

Table 4.18: Summary of adverse events for SPRINT Phase II Stratum I

Adverse events	Selumetinib (N=50)
All grade AEs, n (%)	[redacted]
Grade ≥3 AEs, n (%)	[redacted]
Treatment-emergent grade ≥3 AEs, n (%)	[redacted]
SAEs, n (%)	[redacted]
Treatment-emergent SAEs[a], n (%)	[redacted]
Deaths, n (%)	[redacted]
Dose interruptions due to AEs, n (%)	[redacted]
Dose reductions due to AEs, n (%)	[redacted]
Discontinuations due to AEs, n (%)	[redacted]

Based on Table C23 of the CS[1] which in turn is based on the 90 day safety update[73]
[a] As assessed by the investigator and including possibly, probably, or definitely related to selumetinib treatment.
AE = adverse event; CS = company submission; SAE = serious adverse event

A summary of the most common AEs (experienced by at least 50% of patients) experienced in SPRINT Phase II Stratum I is presented in Table 4.19. The two most common AEs were [redacted].[73]

Table 4.19: Common adverse events for SPRINT Phase II Stratum I

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Vomiting	[redacted]
Blood creatine phosphatase increased	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]
Dry skin	[redacted]
Pyrexia	[redacted]
Fatigue	[redacted]

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Dermatitis acneiform	[redacted]
Hypoalbuminaemia	[redacted]
Headache	[redacted]
Oropharyngeal pain	[redacted]
Stomatitis	[redacted]

Based on Table C24 of the CS[1] which in turn is based on the 90 day safety update.[73]
Table is sorted by frequency for preferred terms at DCO for 90 day safety update and includes events experienced by ≥50% of patients. Patients with multiple events in the same PT are only counted once in that PT. Patients with events in more than one PT were counted once in each of those PTs. Includes AEs with and onset date on or after the first dose and up to and including 30 days following the last dose of selumetinib. MedDRA version 21.0.
AE = adverse event; CS = company submission; DCO = data cut off; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

The ERG asked the company to provide further data on common AEs i.e., those experienced by more than 5% and more than 10% of participants. The company provided a table of AEs of any grade experienced by more than 10% of participants, reproduced in Table 4.20.[53] The company stated that the corresponding data for more than 5% of participants were not available but could be gleaned from individual patient records.[74]

Table 4.20: Adverse events of any grade experienced by >10% of patients for SPRINT Phase II Stratum I

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Vomiting	[redacted]
Blood creatine phosphatase increased	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]
Dry skin	[redacted]
Pyrexia	[redacted]
Fatigue	[redacted]
Dermatitis acneiform	[redacted]
Hypoalbuminaemia	[redacted]
Headache	[redacted]
Oropharyngeal pain	[redacted]
Stomatitis	[redacted]
Pruritis	[redacted]
Abdominal pain	[redacted]
Anaemia	[redacted]
Paronychia	[redacted]
Aspartate aminotransferase increased	[redacted]
Abdominal pain upper	[redacted]
Cough	[redacted]
Rash maculo-papular	[redacted]

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Constipation	[redacted]
Nasal congestion	[redacted]
Pain in extremity	[redacted]
Alanine aminotransferase increased	[redacted]
Neutrophil count decreased	[redacted]
Hypoglycaemia	[redacted]
Influenza-like illness	[redacted]
Lipase increased	[redacted]
Pain	[redacted]
Rhinitis allergic	[redacted]
Blood creatinine increase	[redacted]
Dizziness	[redacted]
Epistaxis	[redacted]
Fall	[redacted]
Haematuria	[redacted]
Otitis media	[redacted]
Decreased appetite	[redacted]
Eczema	[redacted]
Hypocalcaemia	[redacted]
Hypokalaemia	[redacted]
Lymphocyte count increased	[redacted]
Alopecia	[redacted]
Ejection fraction decreased	[redacted]
Hair colour changes	[redacted]
Hyperglycaemia	[redacted]
Proteinuria	[redacted]
Blood alkaline phosphatase increased	[redacted]
Hyperkalaemia	[redacted]
Lymphocyte count decreased	[redacted]
Upper respiratory tract infection	[redacted]
Amylase increased	[redacted]
Haemoglobin increased	[redacted]
Insomnia	[redacted]
Sinus tachycardia	[redacted]
White blood cell count decreased	[redacted]
Back pain	[redacted]
Hypernatraemia	[redacted]
Hypertension	[redacted]
Pharyngitis	[redacted]

AEs, preferred term	All grade AEs, selumetinib (N=50), n (%)
Hyponatraemia	[redacted]
Hypophosphataemia	[redacted]
Lacrimation increased	[redacted]
Neck pain	[redacted]
Skin infection	[redacted]
Dehydration	[redacted]
Pharyngitis streptococcal	[redacted]
Urinary incontinence	[redacted]
Anxiety	[redacted]
Ear pain	[redacted]
Hypersensitivity	[redacted]
Oedema peripheral	[redacted]
Platelet count decreased	[redacted]
Rhinorrhoea	[redacted]
Sinusitis	[redacted]
Abdominal distention	[redacted]
Arthralgia	[redacted]
Cellulitis	[redacted]
Conjunctivitis	[redacted]
Hypermagnesaemia	[redacted]
Hypomagnesaemia	[redacted]
Localised oedema	[redacted]
Weight increased	[redacted]
Based on Table 4 of the response to the request for clarification[53] which in turn is based on the 90 day safety review[73] AE = adverse event	

Table 4.21 summarises the data on Grade ≥3 AEs using the Common Terminology Criteria for Adverse Events (CTCAEs; no reference provided in the CS). Overall, Grade ≥3 AEs were reported in [redacted] of selumetinib-treated patients.[73] AEs of Grade ≥3 were most commonly reported [redacted]. By preferred term (PT), the most commonly reported AEs of Grade ≥3 were [redacted].

Table 4.21: Adverse events for CTCAE for SPRINT Phase II Stratum I

SOC/MedDRA preferred term	Selumetinib (N=50), n (%)[a]
Patients with AE CTCAE Grade ≥3, n (%)	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Vomiting	[redacted]
Dental caries	[redacted]
Nausea	[redacted]

SOC/MedDRA preferred term	Selumetinib (N=50), n (%)[a]
Investigations	[redacted]
Weight increased	[redacted]
Blood creatine phosphokinase increased	[redacted]
Alanine aminotransferase increased	[redacted]
Lipase increased	[redacted]
Infections and infestations	[redacted]
Paronychia	[redacted]
Skin and subcutaneous tissue disorder	[redacted]
Dermatitis acneiform	[redacted]
Eczema	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Reparatory, thoracic and mediastinal disorders	[redacted]
Hypoxia	[redacted]
Nervous system disorders	[redacted]
Syncope	[redacted]
Blood and lymphatic system disorders	[redacted]
Anaemia	[redacted]

Based on Table C25 of the CS[1] which in turn is based on the 90 day safety update[73]
Footnote: Table includes AEs of Grade ≥3 which were reported in ≥2 patients, with an onset date on or after the date of first dose and up to and including 30 days following the last dose of selumetinib. MedDRA version 21.0, CTCAE version 4.0. [a] Each patient has only been represented with the maximum reported CTCAE grade for each system organ class/preferred term.
AE = adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class

Serious adverse events (SAEs), classified as important medical events, were reported in [redacted] selumetinib-treated patients (summarised in Table 4.22).[73] [redacted] SAEs were known adverse drug reactions (ADRs, i.e. AEs which have been identified as causally related to treatment) for selumetinib ([redacted]).

Table 4.22: Summary of SAEs related to selumetinib reported in ≥2 patients for SPRINT Phase II Stratum I

System organ class and preferred term	Selumetinib (N = 50), n (%)
Patients with any SAE	[redacted]
Patients with any SAE causally related to treatment[a]	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Blood and lymphatic system disorders	[redacted]
Anaemia	[redacted]

System organ class and preferred term	Selumetinib (N = 50), n (%)
Respiratory, thoracic and mediastinal disorders	[redacted]
Hypoxia	[redacted]

Based on Table C26 of the CS[1] which in turn is based on the 90 day safety update[73]
Footnote: Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of selumetinib. [a] As assessed by the investigator and including possibly, probably or definitely related to selumetinib treatment.
AE = adverse event; CS = company submission; SAE = serious adverse event

[redacted] experienced a MPNST as an SAE, involving the malignant transformation of a PN; none were considered to be related to selumetinib treatment.[32, 73] [redacted][32] [redacted][32] [redacted][73]

At the data cut-off on 29 March 2019 (90 day safety update), except for [redacted], all SAEs had resolved with either no action taken, following a dose interruption or delay/dose reduction, or following selumetinib discontinuation.[32, 73]

Table 4.23 summarises adverse events of special interest (AESIs). In the CS, the company explained that prior to database lock, certain medical concepts and PTs were defined as being AESIs, based on the established effects of MEK inhibition, non-clinical findings, and emerging data from ongoing clinical studies with selumetinib. The CS went on to say that AESIs were [redacted], and generally resolved whilst on selumetinib treatment, with dose modification and/or with supportive therapy.[1, 73]

Table 4.23: Adverse events of special interest for selumetinib for SPRINT Phase II Stratum I

AEs	Selumetinib (N = 50), n (%)
Patients with any AESI	[redacted]
Grade ≥3	[redacted]
Erythropaenic effects[a]	[redacted]
Grade ≥3	[redacted]
Leukopaenic effects[b]	[redacted]
Grade ≥3	[redacted]
Thrombocytopaenic effects[c]	[redacted]
Grade ≥3	[redacted]
Cardiac events[d]	[redacted]
Grade ≥3	[redacted]
Muscular events[e]	[redacted]
Grade ≥3	[redacted]

AEs	Selumetinib (N = 50), n (%)
Physeal dysplasia	[redacted]
Grade ≥3	[redacted]
Nail disorders[f]	[redacted]
Grade ≥3	[redacted]
Oral mucositis effects[g]	[redacted]
Grade ≥3	[redacted]
Rash acneiform[h]	[redacted]
Grade ≥3	[redacted]
Rash non-acneiform[i]	[redacted]
Grade ≥3	[redacted]
Retinal events[j]	[redacted]
Grade ≥3	[redacted]

Based on Table C27 of the CS[1] which in turn is based on the 90 day safety update[73]
Footnote: PTs reported: [a] Anaemia. [b] Lymphocyte count decreased, neutrophil count decreased, white blood cell count decreased. [c] Platelet count decreased. [d] Ejection fraction decreased, oedema peripheral, peripheral swelling, right ventricular ejection fraction decreased. [e] Acute kidney injury, blood creatine phosphokinase increased, blood creatinine increased, hypocalcaemia, muscular weakness, musculoskeletal pain, myalgia. [f] Paronychia. [g] Mouth ulceration, stomatitis. [h] Dermatitis acneiform. [I] Pruritus, rash, rash erythematous, rash maculo-papular, rash pruritic. [j] Chorioretinal scar, photophobia, vision blurred, vitreous disorder
AE = adverse event; AESI = adverse event of special interest; CS = company submission; PT = preferred term

In the CS, the company outlined some information about dose interruptions, reductions, and discontinuations for SPRINT Phase II Stratum I.

Dose interruptions

Whilst dose interruptions occurred in [redacted], single missed doses were counted as dose interruptions, contributing to the relatively high number of interruptions recorded. The most common reasons for dose interruptions were ‘[redacted] Dose interruptions of selumetinib due to AEs occurred in [redacted]. The most common AEs (reported in >5 patients) that resulted in treatment interruption were [redacted] the majority of which are ADRs for selumetinib.[1, 73]

Dose reductions

In total, [redacted] had dose reductions due to AEs; the majority of AEs that were causally attributed to selumetinib and led to dose reduction were Grade ≥3. All of the AEs which required a dose reduction resolved and were managed with symptomatic and/or supportive treatment where necessary. The selumetinib ADRs which lead to dose reductions included [redacted].[1, 73]

Discontinuation

Discontinuation of selumetinib due to AEs occurred in [redacted]. [redacted] resolved after selumetinib was stopped; [redacted] at the data cut-off on 29th March 2019 (90 day safety update). The most common system organ class AEs leading to permanent discontinuations was [redacted][1, 73]

As a priority question, the ERG asked the company to provide further information on the AEs that led to treatment discontinuation.[57] In response, the company tabulated the frequencies of different types of AEs leading to treatment discontinuation and outlined information relating to each affected participant (Tables 4.24 and 4.25 respectively).[53] Table 4.24: Adverse events leading to discontinuation of selumetinib, by system organ class and preferred term for SPRINT Phase II Stratum I

System organ class/Preferred term	Selumetinib (N=50), n (%)[a]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted][b]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Based on Table 17 of the response to the request for clarification[53] which in turn is based on the 90 day safety update[73]

[a] Number (%) of patients with an AE leading to discontinuation of selumetinib, sorted by international order for SOC and alphabetically for PT. Patients with multiple AEs leading to discontinuation of selumetinib are counted once for each SOC/PT.[53]

[b] [redacted][53, 74]

AE = adverse event; MPNST = malignant peripheral nerve sheath tumour; PT = preferred term; SOC = system organ class

Table 4.25: Description of adverse events leading to discontinuation of selumetinib, per individual participant for SPRINT Phase II Stratum I

Patient identification	Description of AE leading to treatment discontinuation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted][43]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Based on Table 18 of the response to the request for clarification[53] which in turn is based on individual patient reports[74]
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MPNST = malignant peripheral nerve sheath tumour; PN = plexiform neurofibroma; SAE = serious adverse event

Two additional studies provided data on AEs.[55, 56] Details are provided in the following Sections.

4.2.4.2.2 Adverse events associated with selumetinib reported in Baldo et al. 2020

The frequencies of different types of AEs for Baldo et al. 2020 are shown in Table 4.26.[55] Nine participants were recruited to a single-centre study. The mean age of participants was 11 years (range four to 18 years). All participants received selumetinib twice daily with minimum and maximum doses being 20 mg/m^2 and 25 mg/m^2, respectively. The mean length of follow-up was 12 months (range 3 to

26 months). With the exception of ischaemic stroke, all AEs were described as 'minor'. None of the participants discontinued treatment because of AEs.[55]

Table 4.26: Adverse events reported during treatment with selumetinib for Baldo et al. 2020

Adverse event	Selumetinib (N=9), n (%)
Acne[a]	7 (78)
Paronychia[b]	6 (67)
Diarrhoea[c]	6 (67)
Irritability[d]	4 (44)
Raised creatinine kinase[e]	2 (22)
Ischaemic stroke[f]	1 (11)
Mucositis	1 (11)
Sole desquamation	1 (11)

Based on Table 3 of Baldo et al. 2020[55]
[a] All patients treated with benzoyl peroxide or topical clindamycin, none required oral antibiotics. [b] Exclusively involved the toes; all patients initially treated with warm water, salt soaks and gentamycin/betamethasone ointment; 3 patients required surgical partial excision of nail and application of compressive medications. [c] One patient required treatment with loperamide and the selumetinib dose was reduced from 25 mg/m^2 to 20 mg/m^2. [d] Described by parents as not worrisome and not interfering with the child's activities. [e] Two patients presented with creatine kinase of 233 U/L and 321 U/L respectively; both were asymptomatic and never complained of fatigue, pain or other muscular symptoms. [f] Deemed as unrelated to selumetinib treatment.

4.2.4.2.3 Adverse events associated with selumetinib reported in Espirito Santo et al. 2020

Espirito Santo et al. 2020 reported on the grade and type of AEs, summarised in Table 4.27.[56] Nineteen participants were recruited from a single oncology centre. The median age at enrolment was 13 years (range 3 to 19 years). All participants received selumetinib 25 mg/m^2 twice daily. The mean duration of follow-up was 223 days (range 35 to 420 days). All participants reported at least one grade of AE. Selumetinib treatment was suspended in one participant after 168 days because of lack of clinical benefit and occurrence of left ventricular ejection fraction reduction that resolved within a month following suspension.[56]

Table 4.27: Adverse events reported during treatment with selumetinib for Espirito Santo et al. 2020

Number (%) of participants reporting AEs per grade		Description of AEs per grade
CTCAE Grade 1	18/19 (95)	Not reported
CTCAE Grade 2	15/19 (79)	Acneiform rash 7/19 (37) Asymptomatic left ventricular ejection fraction reduction 4/19 (21) Paronychia 3/19 (16) Nausea & vomiting 1/19 (5%) Erythematous rash 1/19 (5%) Neutrophil count decrease 1/19 (5%)
CTCAE Grade 3	2/19 (11%)	Asymptomatic increase in creatine phosphokinase 2/19 (11)

Based on Table 2 and text from Espirito Santo et al. 2020[56]
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

4.2.4.3 Propensity score analysis results

The results of the propensity score matching analyses are presented in Table 4.28. The results were highly consistent across all four additional analyses, demonstrating a high degree of robustness to the choice of method used for comparison.

Kaplan-Meier curves for the analyses (naïve, weighted, matched 1:1 without replacement, and matched 1:2 with replacement) are presented in the appendices of the CS.[1]

Table 4.28: HR for PFS for the naïve comparison and for the propensity score analyses

Analysis	Hazard Ratio[a]	95% CI	P-value
Cox model: Naïve comparison	[redacted]	[redacted]	[redacted]
Cox model: Matched patients 1:1 (robust variance estimator)[b,c]	[redacted]	[redacted]	[redacted]
Cox model: Weighted by stabilised IPTW	[redacted]	[redacted]	[redacted]
Cox model: Weighted by IPTW (robust variance estimator)	[redacted]	[redacted]	[redacted]
Cox model: Matched patients 1:2 (robust variance estimator)[c,d]	[redacted]	[redacted]	[redacted]

Based on Table C29 of the CS[1]

[a] HRs were obtained using Cox regression with study as the only covariate; [b] Greedy Matching algorithm is used without replacement. [c] The difference in the logit of the propensity score for a match must be ≤0.2 times the pooled estimate of the common standard deviation of the logits of the propensity scores. [d] Each treated patient is matched up to 2 controls. Matching is performed with replacement.

CI = confidence interval; CS = company submission; HR = hazard ratio; IPTW = inverse probability of treatment weighting; PFS = progression-free survival

ERG comment: Given the lack of comparative studies, the ERG agrees with the general methodological approach and these methods are consistent with TSD 17.[75]The company also showed the robustness to variation in methods. It might also be useful to have employed multivariate regression in order to further test the robustness of the results.

It should be noted that PFS was not listed as a outcome of interest in the NICE final scope, as discussed in Section 4.2.4.1.10.[54] Therefore, the ERG requested propensity score analyses of the two outcomes, PN growth rate and ORR, which the company provided in response to the clarification letter (Tables 4.29 to 4.31). As can be seen, in Table 4.29, data from the Natural History study showed an ORR of 0%, making the results of a propensity score adjusted comparison a foregone conclusion. As shown in Tables 4.30 and 4.31, the superiority of selumetinib was demonstrated in terms of growth rate, either as percentage change or absolute value, which was robust to variation in method of propensity score analysis.

Table 4.29: ORR from propensity score-adjusted patient populations of SPRINT and NH studies

Propensity score adjustment method	Group	n	Number (%) of patients with response	95% CI**
1:1 match	SPRINT	37	[redacted]	[redacted]
	NH	37	[redacted]	[redacted]
1:2 match	SPRINT	46	[redacted]	[redacted]
	NH	43	[redacted]	[redacted]

IPTW	SPRINT	129.1*	[redacted]	[redacted]
	NH	122.1*	[redacted]	[redacted]
Stabilised IPTW	SPRINT	51.6*	[redacted]	[redacted]
	NH	73.3*	[redacted]	[redacted]

Source: Table 5, CL
* Sum of weights from propensity score
** The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
CI: confidence interval; IPTW: Inverse Probability of Treatment Weighting; NH: Natural History; PN: plexiform neurofibroma.

Table 4.30: Percentage change in target PN volume (mean difference by propensity score adjustment method) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Propensity score adjustment method	Group	n	Time period, years, Mean (95% CI)	PN volume % change/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1:1 match	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
1:2 match	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
IPTW	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]
Stabilised IPTW	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean difference				[redacted]

Source: Table 6, CL
CI: confidence interval; IPTW: Inverse Probability of Treatment Weighting; NH: Natural History; PN: plexiform neurofibroma.

Table 4.31: Absolute change in target PN volume (mean difference by propensity score adjustment method) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Propensity score adjustment method	Group	n	Time period, years, Mean (95% CI)	PN volume change(ml)/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1:1 match	SPRINT	[redacted]	[redacted]	[redacted]	[redacted]

	NH	[redacted]	[redacted]	[redacted]
	Adjusted mean difference			[redacted]
1:2 match	SPRINT	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]
	Adjusted mean difference			[redacted]
IPTW	SPRINT	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]
	Adjusted mean difference			[redacted]
Stabilised IPTW	SPRINT	[redacted]	[redacted]	[redacted]
	NH	[redacted]	[redacted]	[redacted]
	Adjusted mean difference			[redacted]

Source: Table 7, CL
CI: confidence interval; IPTW: Inverse Probability of Treatment Weighting; NC: not calculable; NH: Natural History; PN: plexiform neurofibroma.

4.3 Results of the ITC

No indirect treatment comparison (ITC) was presented in the CS.[1]

4.4 Additional work on clinical effectiveness undertaken by the ERG

As detailed in Section 4.2.1, the ERG assessed the relevance of all studies identified by the SLR reported in CS.[1] Two additional studies were considered to be relevant to the NICE final scope.[55, 56] The validity assessment was checked (see Section 4.2.3) and the results regarding AEs presented (see Section 4.2.4.2).

4.5 Conclusions of the clinical effectiveness section

4.5.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

As reported in Section 4.1.1, the company searched a broad range of resources, including supplementary searches of conference proceedings and other relevant resources such a trials database, company records and the checking of references lists to identify additional studies not retrieved by the main searches. Individual strategies were well constructed and contained a combination of subject heading index and free text terms. Searches were clearly reported and reproducible. A few minor errors were identified; however, these are unlikely to have impacted on the findings of the literature reviews.

As detailed in Section 4.2.1, the ERG considered two additional studies to be relevant to the NICE final scope.[55, 56] These provided further results regarding AEs.

4.5.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator, and outcomes

Clinical efficacy results were presented from the SPRINT Phase II Stratum I trial (recruiting 50 patients from four centres in the USA), and comparisons were made with the NCI Natural History study (93 age-matched individuals) and the placebo arm of the tipifarnib study (29 participants). These are reported in Section 4.2.4 and summarised below:

- Results suggested that more participants receiving selumetinib in SPRINT Phase II Stratum I experienced a reduction in PN volume of at least 20% when compared with usual care in the NCI National History study (68% vs. 0%).
- 45 patients (90%) treated with selumetinib in SPRINT Phase II Stratum I had BOR of reduction in PN volume from baseline, and 37 patients (74%) experienced at least 20% reduction in PN volume at BOR.
- The median time to initial response in SPRINT Phase II Stratum I was 8 cycles (range 4 to 20), and the median time to best response was 16 cycles (range 4 to 36).
- None of the participants receiving selumetinib in SPRINT Phase II Stratum I displayed a PN growth rate of 20% or more per year (range -27.0% to 19.8% per year), compared with 43% of patients in the age-matched cohort of the NCI Natural History study.
- The median PFS was not reached in SPRINT Phase II Stratum I at DCO 29th March 2019. At 3 years, 84% of patients in SPRINT Phase II Stratum I remained progression-free compared with 15% in the NCI Natural History age-matched cohort.

With respect to safety and AEs, at a DCO of 29 March 2019 for the SPRINT Phase II Stratum I study, [redacted] of patients experienced AEs, [redacted] of patients experienced Grade ≥3 AEs, and [redacted]. Results for two additional studies, reporting on 28 participants, are in line with these findings, details can be found in Section 4.2.4.2.

As there were no head-to-head trials comparing selumetinib to established clinical management, naïve comparisons were conducted between SPRINT Phase II Stratum I, an age-matched cohort from the NCI National History study, and the placebo arm of the tipifarnib study. In addition, to explore the potential impacts of adjusting for baseline covariates across the study population, the company undertook a propensity score analysis. The results showed a statistically significant advantage of selumetinib compared to 65 participants of the Natural History age-matched cohort, e.g. [redacted]. Results were highly consistent across all four additional analyses and demonstrated a high degree of robustness to the choice of method used for comparison. However, these results were based only on PFS, where progression was defined as ≥20% increase in PN volume, which was not listed in the NICE final scope. Therefore, on request by the ERG the company supplied propensity score analyses of PN growth rate, which also showed a clear advantage to selumetinib regardless of choice of method used for the comparison.

4.5.3 Uncertainties surrounding the clinical effectiveness

The ERG identified a few weaknesses and uncertainties related to the clinical effectiveness:

- The clinical effectiveness evidence comes from small single-arm studies.
- The SLR conducted for the clinical effectiveness section does not follow best practice.
- Two additional studies, identified by the company, are relevant to the DP.
- The size of the total population eligible for selumetinib might be bigger than indicated in the CS.

- Participants of SPRINT Phase II Stratum I were recruited in the USA which might limit the generalisability to patients in the UK.

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

This chapter provides an assessment of whether selumetinib for treating symptomatic, inoperable PNs associated with NF1 represents value for money for the NHS in England. The main source of evidence used to inform this assessment is the CS and the electronic cost effectiveness model. This chapter provides a summary of the literature review performed by the company to search for economic evidence, the structure of the economic model, the evidence used to inform the input parameters of the economic analyses, the results of the company cost effectiveness analyses (CEAs) and a critique of all these aspects conducted by the ERG.

5.2 Review of existing economic analyses

Appendix 4 (Section 17.4) of the CS reported a single set of literature searches used to identify relevant published literature on HRQoL, cost and resource use, and economic evaluations.[1]

5.2.1 Searches

Searches were conducted between January and February 2021. A summary of the resources searched are provided in Table 5.1. The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.

Table 5.1: Resources searched for cost effectiveness evidence. January/February 2021

Resource	Host/Source	Date Range	Date searched
Databases			
Embase	Ovid	1974-2021/01/25	26.1.21
MEDLINE & MEDLINE In-Process	Ovid	1946-2021/01/25	26.1.21
HTA database	CRD	Up to 2016/10/Iss4	26.1.21
NHS EED	CRD	Up to 2005/04/Iss2	26.1.21
INAHTA	Internet	Up to 2021/01/25	26.1.21
Conference Proceedings			
ISPOR (International & European meetings)		2018-2020	5.2.21
JGNC (Children's Tumor Foundation NF + European Neurofibromatosis)		2018	5.2.21
Children's Tumor Foundation NF		2019-2020	5.2.21
ESMO		2018-2020	5.2.21
ASCO		2018-2020	5.2.21
ISPNO		2018 & 2020	5.2.21
ASPHO		2018-2020	5.2.21
HTA body websites			
AWMSG		2011–2021	22.1.21
NCPE		2011–2021	22.1.21
NICE		2011–2021	22.1.21

Resource	Host/Source	Date Range	Date searched
SMC		2011–2021	22.1.21
Specialist Websites			
CEA registry		All	22.1.21
ScHARRHUD		All	22.1.21
EQ-5D publications database		All	22.1.21
PEDE		All	22.1.21
Additional searches			
Manual searches of materials provided by AZ			
Manual searches of the bibliographies of all relevant SLRs, [N]MAs), HTAs and economic evaluations identified during the course of the review			

ASCO = American Society of Clinical Oncology; ASPHO = American Society of Pediatric Hematology/Oncology; AWMSG = All Wales Medicines Strategy Group; AZ = AstraZeneca; CEA = cost effectiveness analysis; EED = Economic Evaluation Database; EQ-5D = European Quality of Life-5 Dimensions; ESMO = European Society for Medical Oncology; HTA = health technology assessment; INAHTA = International Network of Agencies for Health Technology Assessment; ISPNO = International Symposium on Pediatric Neuro-Oncology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; JGNC = Joint Global Neurofibromatosis Conference; MA = meta-analysis; NCPE = National Centre for Pharmacoeconomics; NHS = National Health Service; NF = neurofibromatosis; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PEDE = Paediatric Economic Database Evaluation; ScHARRHUD = University of Sheffield Health Utilities Database; SLR = systematic literature review; SMC = Scottish Medicines Consortium

ERG comment:

- An extensive range of resources (including bibliographic databases and grey literature resources) were searched for the economic SLR, and searches were clearly reported and reproducible.
- Individual strategies were well constructed and contained a combination of subject heading index and free text terms. The conditions facet was broader than that used for the clinical effectiveness section in order to maximise recall.

5.2.2 Review process and results

The eligibility criteria for the economic SLR are displayed in Table 5.2. Given that there is a small body of evidence surrounding NF1, broad inclusion and exclusion criteria were used.

Table 5.2: Selection criteria used for health economic studies

Domain	Economic evaluations		HRQoL		Cost and resource use	
	Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
Population	Paediatric or adult patients with NF1	Paediatric and/or adult patients without NF1	• Paediatric or adult patients with NF1 with PN • Paediatric or adult patients with NF1 without PN for whom HSUVs are reported[a] • Caregivers/ family of patients with NF1 with PN	• Paediatric and/or adult patients without NF1 • Paediatric or adult patients with NF1 without PN for whom only HRQoL values are reported[a]	• Paediatric or adult patients with NF1 with PN • Caregivers/ family of patients with NF1 with PN	• Paediatric and/or adult patients without NF1 • Paediatric or adult patients with NF1 without PN[b]
Intervention	Any or none					
Comparator	Any or none					
Outcomes	• ICERs • Cost per clinical outcome • Total QALYs • Total DALYs • Total LYGs • Total costs • Incremental costs and QALYs/ DALYs	Studies not presenting relevant outcomes for the population of interest	Any utilities or HRQoL data, if measured by a formal validated tool or instrument, including but not limited to: • EQ-5D-5L • Standard gamble • Time trade-off • SF-36 • PedsQL (including NF1 module) • PROMIS • TACQOL	Studies not presenting relevant outcomes for the population of interest	Direct costs and resource use, including: • Drug cost • Administration cost • Hospitalisation cost • Monitoring costs Indirect costs and resource use, including: • Productivity loss • Home adaptation • Travel costs	Studies not presenting relevant outcomes for the population of interest

Domain	Economic evaluations		HRQoL		Cost and resource use	
	Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
Study design	• Cost-utility • Cost effectiveness • Cost-consequence • Cost-benefit • Cost-minimisation	Any other types of analysis	Any original research study	N/A	Any original research study including budget impact models and cost-of-illness studies	N/A
	SLRs or (N)MAs of relevant study designs were included at the title/abstract screening stage for the purpose of identifying any additional studies not identified in the database searches but were ultimately excluded at the full-text review stage.					
Publication type	**Inclusion**: • Journal articles presenting original research • HTAs • Conference abstracts published in or since 2018 **Exclusion**: • Articles not presenting original research, e.g., narrative reviews, guidelines, commentaries or opinion pieces, editorials • Conference abstracts published before 2018					
Other considerations	**Inclusion**: • Human subjects • Any geographic location **Exclusion**: • In vitro/ preclinical studies/animal studies					

Based on Table D1 of the CS[1]

[a] Records that presented any HRQoL values for paediatric or adult patients with NF1 without PN were included at title/abstract review then excluded at full-text review due to the high volume of relevant data identified; records presenting HSUV values for paediatric or adult patients with NF1 without PN were included at both review stages;

[b] Records that presented any CRU data for paediatric or adult patients with NF1 without PN were included at title/abstract review then excluded at full-text review due to the high volume of relevant data identified.

Domain	Economic evaluations		HRQoL		Cost and resource use	
	Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
CS = company submission; DALY = disability-adjusted life-year; EQ-5D-5L = EuroQoL-5 dimensions-5 levels; HRQoL = health-related quality of life; HSUV = health-state utility value; HTA = health technology assessment; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NF1 = type 1 neurofibromatosis; PedsQL = Pediatric Quality of Life Inventory; PN = plexiform neurofibroma; PROMIS = Patient-Reported Outcomes Measurement Information System; QALY = quality-adjusted life-year; SF-36 = Short Form 36; SLR = systematic literature review; TACQOL = Netherlands Organization for Applied Scientific Research Academic Medical Centre (TNO AZL) Children's Quality of Life						

The PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram is presented in Figure D1 of the CS.[1] The electronic search resulted in 794 records, of which 539 were unique records screened at the title and abstract level. Of these, 108 were screened at full text. Full text review resulted in eight studies being included in the HRQoL SLR, three included in the cost and resource use SLR and none in the economic evaluation SLR. A list of included studies as well as those studies excluded at full text stage alongside reasons for exclusion is provided in Section 17.4.8 of the CS.[1]

ERG comment: The ERG considers the systematic review to be well conducted.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

Table 5.3 provides an assessment of the adherence of the company model to the NICE reference case.

Table 5.3: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE.	As per reference case.
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice.	In line with the final scope, BSC is the only comparator. BSC is defined as current clinical management of patients with NF1 PN, which is limited to symptomatic management.
Perspective on costs	NHS and PSS.	As per reference case.
Perspective on outcomes	All health effects on individuals.	Health effects on individuals and caregivers included.
Type of economic evaluation	Cost effectiveness analysis.	As per reference case.
Time horizon	Sufficient to capture differences in costs and outcomes.	Lifetime perspective adopted.
Synthesis of evidence on outcomes	Based on a systematic review.	An SLR was conducted as per the reference case.
Measure of health effects	QALYs and life years.	Health outcomes are valued in terms of life years and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers.	The health state utility values used in the model were not estimated via HRQoL data measured by patient or carer self-

Element of economic analysis	Reference case	ERG comment
Source of preference data for valuation of changes in HRQoL	Representative sample of the public.	reports. Vignettes describing health states were valued directly by members of the UK general population without patient measurement. Therefore, while the valuation aspect of the reference case was met, the measurement element was not.
Discount rate	An annual rate of 3.5% on both costs and health effects.	As per the reference case.
Equity weighting	An additional weighting can be applied for incremental QALYs above 10 years.	No additional weighting applied.

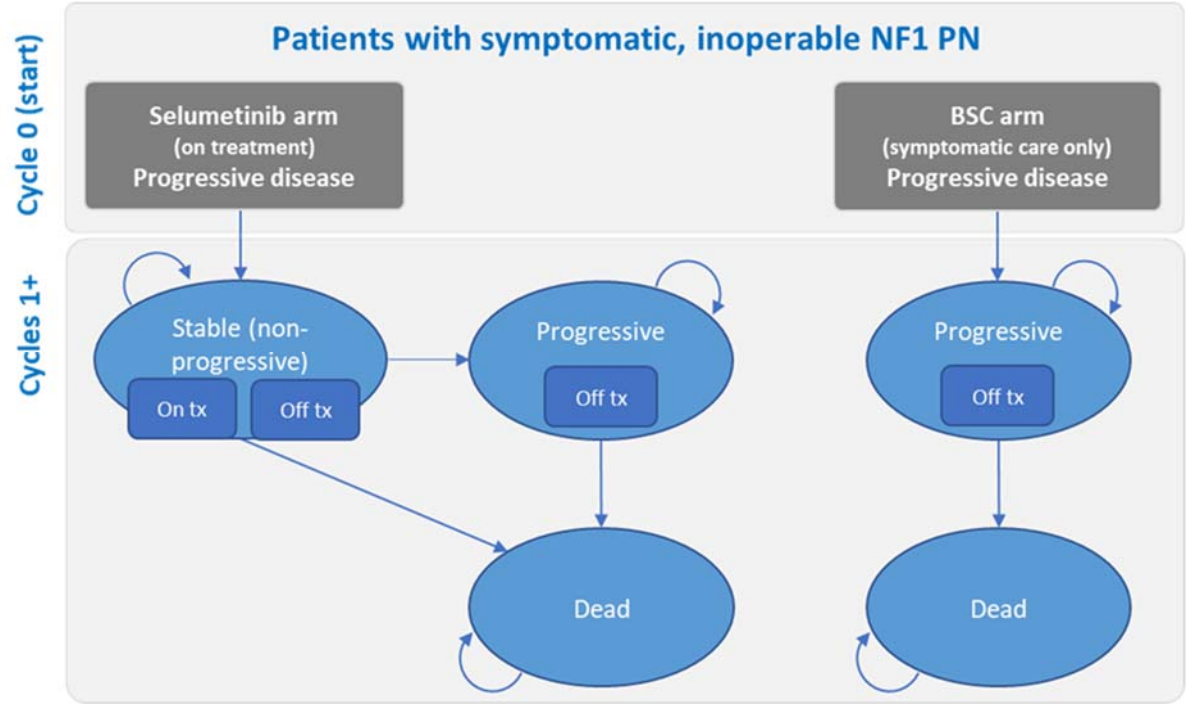
BSC = best supportive care; ERG = Evidence Review Group; HRQoL = health-related quality of life; NF1 = type 1 neurofibromatosis; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PN = plexiform neurofibroma; PSS = personal social services; QALYs = quality-adjusted life years; UK = United Kingdom

5.3.2 Model structure

A de novo area-under-the-curve (AUC) model structure, also known as a partioned survival model, was developed to assess the cost effectiveness of selumetinib in NF1 PN. Key assumptions were validated by UK clinical experts in NF1 PN. The model, shown in Figure 5.1, consists of three health states, which are defined based on the natural history of disease progression as either stable/non-progressive disease (stabilised or reduced PN growth), progressive disease (defined as ≥20% increase in size from baseline of PN or, if a patient had had a PR, an increase of at least 20% from the best response, by volumetric MRI analysis in line with the REiNS criteria) or death. Transitions are assumed to occur at each 1-year cycle over a lifetime horizon.

Patients in the best supportive care (BSC) arm enter the model at the progressive disease health state and are assumed to receive pain medications and treatment for symptom relief only. Patients in the selumetinib arm also enter the model at the progressive disease health state but are assumed to experience disease stabilisation within the first year of treatment and remain in the progression-free state until disease progression. Treatment duration was also included in the model, i.e. patients remain on treatment until discontinuation. Given the paediatric license for selumetinib, maximum duration of treatment was assumed until patients reach the age of 18 years. Mortality rates were informed by UK life tables with the addition of a standardised mortality ratio (SMR) to account for a reduced life expectancy associated with NF1-related comorbidities (the company indicated that a PN-specific rate was not available from the literature). No benefit of selumetinib on mortality was assumed. Utility values depend on progression status and are adjusted for age-related disutilities. The utility values associated with current clinical management and selumetinib are assumed to be proxies for progressed and non-progressed health states, respectively. Patients in the selumetinib arm accrue treatment costs (while on selumetinib treatment), AE costs and MRI costs. Patients in the BSC arm accrue costs of current clinical management only (pain medications and treatment for symptom relief).

Figure 5.1: Model structure



Based on Figure 2 of the response to request for clarification[53]
BSC = best supportive care, NF1 = type 1 neurofibromatosis, PN = plexiform neurofibroma, tx = treatment

ERG comment: As mentioned in clarification question B2, the ERG has concerns regarding the type of model used for the submission.[57]

Progressive PN growth is associated with an increase in the number and severity of morbidities over time, resulting in a corresponding decrease in HRQoL. However, number and severity of morbidities are not included in the model. Also, throughout the CS, the heterogeneity of NF1 and PN is emphasised.[34-36, 47] The evidence provided also suggests that disease progression strongly varies with age, and that patient an disease characteristics like age, PN volume or number of PN-related morbidities are expected to be treatment effect modifiers.[7, 11, 23, 25, 76] It should be emphasised that not all of these associations are captured by the current model. The ERG is aware of the limitations of the SPRINT data, but the company could have attempted to study some of those associations on natural history data.

The company justified the choice of the current model structure because "*taking into consideration the progressive natural history of NF1 PN, disease heterogeneity and limited data availability, a simplified AUC approach is the most appropriate structure for estimating the cost-effectiveness of selumetinib compared with current clinical management*".[1] For the reasons explained above, the ERG feels the choice of the model structure was not sufficiently justified. The company further states that this approach "*presents the most realistic and reliable analysis for patients with NF1 PN and reduces the number of additional assumptions that would otherwise be required by alternative model structures. Under these data constraints, it was not feasible to adequately represent NF1 PN in terms of mutually exclusive disease states (e.g., as part of a Markov state-transition model) or as a series of events (e.g., for a patient-level simulation)*".[1]

The ERG acknowledges again the limitations of the available data from SPRINT and agrees with the company that robust statistical analyses are challenging. However, it should be emphasised that the same data were used to inform the AUC model. Therefore, the ERG is not convinced that this approach provides a reliable estimate of the cost-effectiveness of selumetinib. If data are limited (to inform more

complex models), the same limitations and uncertainties are present in the AUC model. Also, while it can be argued that AUC models minimise the number of assumptions required compared with more complex models, this does not imply that the assumptions made for the AUC model are automatically valid. An example of this is given in Section 5.3.3.3 with the modelling of PFS. In conclusion, the AUC choice may seem pragmatic, but the committee should be aware that it also has limitations (like the ones mentioned above) and might rely on strong assumptions and was simplistically implemented (as explained in Section 5.3.3.3). The ERG would argue that a patient-level model, using the same data, but in terms of PN growth rate, might be more useful for decision making.

Similar limitations to those just discussed for survival data, also apply to HRQoL data. The company indicated that no patient-level HRQoL data were available from the Natural History study, which implied that no treatment effect could be determined for selumetinib. Also, given the limited availability of PedsQL data, no robust association could have been identified between for example PN volume or PN growth rate and HRQoL. The company could have tried for example to collect preference-based data from patients and to conduct regression analyses to estimate the relationship between, e.g. PN volume and HRQoL to give an idea of change over time and progression. This is further explained in the ERG critique to Section 5.3.3.7.

Furthermore, as mentioned in clarification question B1, the ERG has concerns regarding the current model structure.[57] The evidence provided in the CS supports the assumption that PFS should also be a health state in the comparator arm of the model. This can be seen for example on page 38 of the CS, Figure C4 and Figure C21 in the CS, on page 94 of the CS, Figure C5 in the CS.[1] This potential issue was raised by the ERG in the clarification letter, however, the company still considered appropriate to assume that patients in the BSC arm stay in the progressive disease health state for the whole duration of the analysis.[1, 57] The ERG considers it appropriate to assume that after progression, BSC patients cannot return to the progression-free health state. The issue is that evidence shows that in the BSC arm there are patients in PFS who do not seem to progress (or to progress slowly) and this is not included in the model.

In response to clarification question B1, the company explained that by "*assigning a constant utility to patients in the progressed state the model likely also underestimates the benefit of selumetinib as it is likely that HRQoL would decline with the increasing PN volume of patients in the progressed health state, the state where BSC patients reside within the model*".[53] The ERG agrees with the company that for patients who progressed a utility lower than the baseline is likely to apply (due to PN progression), but this should also be applied to the selumetinib arm, even though the impact is expected to be minor compared to BSC patients. It should also be emphasised that it seems incorrect to assume that BSC patients are in the progressed health state since the beginning of the simulation.

5.3.3 Evidence used to inform the company's model parameters

This section presents a summary of the evidence sources used to inform the company's model parameters. The main source used in the CS was the SPRINT Phase II Stratum I data.[11, 32] A detailed description of model parameter values and sources is presented below.

5.3.3.1 Population

The patient population considered in the cost effectiveness model is consistent with the licensed population and the DP and can be defined as paediatric patients with NF1 aged 3 years and above with symptomatic, inoperable PN. The key baseline characteristics of patients included in the model are summarised in Table 5.4. These were based on the SPRINT Phase II Stratum I data.[11, 32]

Table 5.4: Baseline characteristics of the modelled population

Parameters	Values	Purpose in the model
Female (%)	[redacted]	Used to implement all-cause mortality data (rates available by female/male)
Age in years (mean [SD])	[redacted]	Tracked in the economic model at each model cycle, affects various inputs (e.g., age-adjusted utility values)
BSA in m^2 (mean [SD])	[redacted]	Required to determine the appropriate dose of selumetinib

Based on Table D2 of the CS[1]
BSA = body surface area; CS = company submission; SD = standard deviation

ERG comment: As discussed in Section 4.2.1, the SPRINT trial has been conducted in the USA, i.e. no UK patients were included.

5.3.3.2 Intervention and comparators

The cost effectiveness of the intervention, selumetinib, is compared against BSC. BSC is defined as current clinical management of patients with NF1 PN, which is limited to symptomatic management. Intervention and comparator are in line with the NICE final scope and DP for this appraisal.[7, 25, 28, 30]

5.3.3.3 Progression free survival

Progression was defined as a tumour volume increase from baseline of at least 20% or an increase of ≥20% from best response if a patient had a PR.[1] A PR was defined as a decrease in the volume of the target PN by ≥20% compared with baseline. Stable disease was defined as a tumour volume change from baseline of less than 20%. Children receiving selumetinib in the SPRINT trial had a higher probability of PFS over 3 years of follow-up compared with the Natural History study age-matched cohort (84% vs. 15%).[1]

Given that only 16% of patients experienced progression during the 3-year SPRINT follow-up, the company considered the data too immature "*to conduct parametric extrapolations*".[1] Therefore, the observed data was used to estimate an annual progression rate of 5.6% per year. Once patients reach the age of 18 years, their tumour size is assumed to stabilise and therefore no progression events are assumed to occur after the age of 18 years. The modelled PFS and time to discontinuation are displayed in Figure 5.2.

Figure 5.2: Modelled PFS (annual probability) and TTD (Weibull) used in the company base-case

Based on Figure D4 of the CS[1]

CS = company submission; PFS = progression-free survival; TTD = time to discontinuation

ERG comment: The ERG requested clarification on whether PFS was defined in terms of one target PN, which would align with the definition of PR and health state vignettes which focus on one lump.[57] In response to the request for clarification, the company confirmed at clarification that progression assessment involved the analysis of one target PN and up to two non-target PN.[53] The target PN was the PN that had been evaluated and deemed to be the most clinically relevant by the treating physician.[77] Since no clinically relevant non-target PN were reported during SPRINT Phase II Stratum I, assessment of progressive disease was based on target PN only.

There is substantial uncertainty in PFS over the long-term due to the immaturity of PFS data and limited follow-up of 3 years. It is unclear how reflective the annual progression probability of 5.6%, which is equivalent to an extrapolation with a simple exponential distribution, is over the long-term. Kaplan Meier curves and fit statistics were not presented, so the fit of this exponential curve to the data available could not be assessed. The ERG believes that, despite the limitations, the company should have attempted to conduct full survival analyses as done with time to treatment discontinuation data (see Section 5.3.3.4).

As discussed in the ERG critique to Section 5.3.2, the ERG considers that the evidence presented by the company shows that in the BSC arm there are patients in PFS who do not seem to progress (or to progress slowly) and yet PFS for the BSC arm has not been in the model. Furthermore, it is unclear why the company have not tried to use for this purpose the results of the propensity score analyses presented in Section 4.2.4.3 of this report. These results were reported as HRs for PFS which in principle could be directly implemented in the economic model, despite the limitation highlighted in aforementioned Section.

The assumption that no progression events occur after the age of 18 years is potentially problematic on two fronts. Firstly, no evidence was presented that progression would never occur over the age of 18 years. Data from the Natural History study presented in Table 13 of the response to request for clarification (in response to question B3) shows that PFS continued to decline (albeit not steeply) to year 5 in patients who started the study aged 16+ (PFS year 1= [redacted]; year 2 = [redacted]; year 3= [redacted]; year 4= [redacted]; year 5 = [redacted]), suggesting some progression events will occur after the age of 18, although fewer events than in the younger age groups.[53] If some progressions would occur in clinical practice, even if only a few, this assumption would favour selumetinib as these patients are artificially held at a higher utility in the model, while all BSC patients are assumed to be progressive.

Secondly, if it is to be accepted that tumour growth does plateau to the extent that no progressions occur after 18 years, then the inclusion of older adolescent patients in the SPRINT trial may have biased results if they would not be expected to progress regardless of treatment, which artificially increases the proportion of patients who remain progression free in the trial and model results.

The company presented data on change in PN volume from the Natural History study, separated by age group in their clarification response, displayed in Figure 5.3.[53] Changes which would be classified as progression or PR in SPRINT are highlighted by red dotted lines. These data show a trend for smaller percentage changes in tumour volume over the age of 12 years, with substantially lower likelihood of progression from the age of 16 years. Therefore, it would appear that patients aged 16 years and above in the SPRINT trial would be unlikely to progress, regardless of treatment. Figure 6 of the response to request for clarification shows that [redacted] SPRINT participants were over the age of 15.5 years.[53]

Figure 5.3: Change in PN growth from NCI Natural History study individual patient profiles, over five years by age group

Based on Figure 7 of the response to request for clarification[53]
NCI = National Cancer Institute; PN = plexiform neurofibroma

The ERG also noted that in Tables 23 and 29 of the CS, which summarise the baseline characteristics of the SPRINT participants in Phase I and Phase II Stratum II, respectively, 9 (38%) and 11 (44%) of patients, respectively, were classed as having progressive PN growth at baseline (defined as ≥20% increase in PN volume within 15 months prior to enrolment).[1] It is unclear whether these patients would have a lower, higher or equivalent chance of experiencing progression during SPRINT compared to those classed as stable at baseline.

5.3.3.4 Treatment discontinuation

Treatment discontinuation was modelled based on parametric extrapolations of patient-level data on TTD from SPRINT Phase II Stratum I. TTD data were observed for a 3-year follow-up period, and extrapolation was needed to estimate TTD for the remaining time period up to a mean age of 18 years. At the beginning of the simulation, all patients within the selumetinib arm are assumed to be on treatment. Once the modelled population reaches a mean age of 18 years, it is assumed that all patients discontinue treatment.

The parametric distributions that were used for the extrapolations of TTD data were the exponential, generalised gamma, Gompertz, loglogistic, lognormal and Weibull. Statistical goodness-of-fit was assessed with Akaike information criterion (AIC) and Bayesian information criterion (BIC). Regression coefficients and AIC and BIC values for the six distributions can be seen in Table 5.5. A plot of the extrapolated curves against the observed data can be seen in Figure 5.4. Selection of the most appropriate distribution was informed by goodness-of-fit statistics, visual inspection of the extrapolated curves and clinical expert opinion. All curves were judged to be similar based on AIC/BIC values and visual inspection of the curves against the trial data. Therefore, final selection was guided by clinical plausibility. From this, the extrapolation using a Weibull distribution was chosen as the most appropriate based on the expectation that discontinuation rates will be highest when patients reach adulthood.

Table 5.5: TTD parameters and goodness-of-fit statistics

Distribution	Parameter	Coefficient	AIC	BIC
Exponential	Intercept	[redacted]	[redacted]	[redacted]
Generalised Gamma	Mu	[redacted]	[redacted]	[redacted]
	Sigma	[redacted]		
	Q	[redacted]		
Gompertz	Shape	[redacted]	[redacted]	[redacted]

	Rate	[redacted]		
Loglogistic	Shape	[redacted]	[redacted]	[redacted]
	Scale	[redacted]		
Lognormal	Meanlog	[redacted]	[redacted]	[redacted]
	Sdlog	[redacted]		
Weibull	Shape	[redacted]	[redacted]	[redacted]
	Scale	[redacted]		

Based on Tables D4 and D5 of the CS[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; TTD = time to discontinuation.
Note: Parametric models were generated in R version 14 using the flexsurv package.

Figure 5.4: TTD parametric extrapolations

[redacted]

Based on Figure D3 of the CS[1]
CS = company submission; TTD = time to discontinuation

ERG comment: The ERG considers the company's approach to the parametric extrapolation of TTD data as appropriate. However, the ERG notes that all extrapolated curves seem to overestimate the number of patients on treatment relative to the observed data from month 20 and onwards. The Weibull curve gives the lowest estimates for the number of patients on treatment and, thus, it is likely to provide the most plausible extrapolation. Furthermore, the ERG would like to note that some counterintuitive results were observed in Section 5.4.2.2; when using extrapolations that estimate a higher number of patients on treatment, the ICER increases, implying that the more patients are treated with selumetinib, the less cost effective it becomes. The explanation for this is that in the economic model, TTD is only linked to costs but not to any clinical benefit; hence, the less patients are on treatment, the lower the costs are, without affecting clinical effectiveness in terms of PFS or HRQoL. According to the ERG, it would have been more appropriate to model an explicit link between TTD and PFS/HRQoL, in such a way that there is a positive relationship between time on treatment and clinical effects, which most likely would not lead to counterintuitive results.

5.3.3.5 Mortality

Mortality was modelled based on general population UK life tables 2016 to 2018 in combination with a SMR of 2.02 (95% CI 1.6 to 2.6) that was sourced from a French cohort study of 1,895 patients with NF1 between 1980 to 2006.[78] The same approach was used for mortality in both treatment arms. Hence, it was assumed that treatment with selumetinib provides no benefits by means of a reduced mortality rate. The company indicated this as a conservative approach, considering the disease modifying nature of treatment with selumetinib and possible impact on mortality rates. Furthermore, it stated that due to data limitations it was not possible to model this potential beneficial aspect of selumetinib.[1, 53]

ERG comment: The ERG considers the modelling of mortality as appropriate. The ERG also agrees with the company that the use of the same mortality rates in both treatment arms may be considered as a conservative approach and that the inclusion of a potential reduction in mortality with selumetinib would otherwise have been surrounded by substantial uncertainty due to data unavailability. The ERG notes that the SMR that was sourced from Duong et al. 2011 pertains to an estimate across all age groups.[78] However, the findings from Duong et al. 2011 indicate that the only significant differences in mortality, i.e. excess mortality, occurred in age groups 10-20 (SMR 5.2) and 20-40 (SMR 4.1).[78]

The ERG would like to note that current cohort model approach does not allow to model excess mortality differently for specific age groups, which would only be possible if these two were linked, e.g. using a patient-level model. As such, the ERG considers the use of an overall SMR across all age groups as appropriate for the current modelling approach.

5.3.3.6 Adverse events

Grade ≥3 AEs that occurred in greater than 5% of patients in SPRINT were included in the model. This included diarrhoea ([redacted]), vomiting ([redacted]), pyrexia (fever, [redacted]), hypoxia ([redacted]), paronychia (infection of the skin around fingernails and toenails, [redacted]) and dermatitis acneiform ([redacted]).[73] Most were of short duration (less than a week), except for paronychia which lasted for a mean duration of [redacted] and dermatitis acneiform which lasted for a mean duration of [redacted]. Table 5.6 summarises the incidences and durations of the included AEs.

Table 5.6: Adverse events reported in SPRINT and included in the economic analysis

Adverse event	Percentage of patients (n/N)	Mean duration, days (SD)
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Pyrexia (Fever)	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]

Based on Table D7 of the CS[1]
CS = company submission; SD = standard deviation

ERG comment: No disutilities were included in the model for these AEs. The ERG requested that these be included at clarification.[57] Given the short duration for all but dermatitis acneiform and the low incidences, it is unlikely that this has a large impact on results, however for completeness these should have been included. In response to the request for clarification, the company noted that the impact of dermatitis acneiform was included in the on-selumetinib health state vignette, so the impact of this AE should be reflected in the valuation.[53]

The ERG noted that [redacted] are reported to have discontinued treatment in SPRINT due to AEs. The ERG asked the company whether and how these discontinuations were incorporated into the model.[57] AEs leading to discontinuation by organ class were shown in Table 16 of the response to the request for clarification.[53] The company explained that [redacted] of the AEs leading to treatment discontinuation were amongst those most commonly experienced in the patient population ([redacted]) and therefore the costs of these events were included in the model.[73] The other four AEs were due to [redacted]. The company noted that after appropriate management all of these AEs resolved.[53] They also noted that PNs are associated with a wide range of morbidities affecting multiple organ systems (dependent on the location and size of the PN) and that in light of the severity of baseline morbidity, and the paediatric population, a [redacted] discontinuation rate due to AEs is not considered substantial.

As discussed in the ERG critique to Section 4.2.1, it is possible that data from two other studies providing data on AEs events could have been included in the CS.[55, 56] However, given that AEs in the model only affected costs and the impact of such costs is almost negligible, the ERG did not explore the option of including these additional data in the model.

5.3.3.7 Health-related quality of life

5.3.3.7.1 HRQoL evidence

HRQoL was measured in the SPRINT Phase II Stratum trial using the PedsQL 4.0 Generic Core Scales. PedsQL is a generic measure of HRQoL that has been validated for use in children and adolescents and the company considered it highly appropriate for capturing patients' experiences on treatment with selumetinib.[79, 80] The company did however note that it does not meet the reference case which prefers the EQ-5D and no published, validated mapping algorithms for the PedsQL that are comparable enough to be applied to the patient population with NF1 PN are available.[1] Additionally the company state that SPRINT only provides data for patients treated with selumetinib and for up to 3 years follow-up, meaning that even if this data were used to estimate utilities, these would not be able to address the disease course of NF1 PN over the entire patient lifetime in the comparative analysis versus current clinical management.[1] Therefore they chose to conduct a vignette study to estimate health state utility values for on and off treatment.

5.3.3.7.2 Vignette/TTO study

The company commissioned a vignette study, in which various vignettes representing different health states associated with patients with NF1 PN were valued using time trade off (TTO) exercises in members of the UK general population. These studies involve two main stages: vignette development and the TTO valuation exercise.

Vignette development

The company report that health state descriptions that appropriately and accurately reflect the disease course of NF1 PN over a patient's lifetime descriptions were informed by a targeted literature review.[1] The targeted literature review informed several key concepts for inclusion in the vignettes: descriptions of the condition (including treatment details, stability of condition and treatment adverse events), symptoms and physical impacts (disfigurement, visual function, bowel and bladder function, motor function and pain) and HRQoL impacts (emotional impact, daily activities, cognitive function, independence).[81] The vignettes developed varied according to PN location (unspecified location, facial, trunk and leg), and treatment status (treated with selumetinib, not treated with selumetinib.[81] The cost

effectiveness model informed the development of two ‘core’ health states (S1: child not treated with selumetinib, S5: child treated with selumetinib).

Feedback on the health state vignettes was sought in interviews with patients (n=8), parents/carers (n=6) and key UK clinical experts in NF1 PN (n=4).[82] Clinical experts were presented with all health state vignettes for review. Adult patients and caregivers were asked to review the one or two health state vignettes that most closely matched their experiences, based on PN location. Adult patients and caregivers only reviewed untreated health state vignettes because they did not have experience relevant to the treated health states (patients and caregivers with experience of selumetinib or other MEK-inhibitors were excluded). Draft vignettes were revised iteratively after interviews with the clinical experts, and subsequently, after adult patient and parent/carer interviews. The final health state vignettes were provided in Appendix A of the TTO study report provided at clarification.[81] The two core health states are shown in Figure 5.5.

Figure 5.5: Core model health state vignettes

Description S1

- You have a life-long genetic condition that causes lumps to grow in any part of the body, causing a range of symptoms. You have one main, large lump with an irregular shape.
- You receive **no active treatment** for your main, large lump. Your condition is monitored by your care team and you receive supportive care to help manage some of your symptoms.
- Your condition is **deteriorating over time**.
- The way you look is affected by your large lump. **Your lump continues to grow**.
- You have some difficulties with movement, strength and coordination. **Your difficulties moving the area around your large lump are deteriorating over time**.
- You **often** experience pain/discomfort in the area around your large lump. The pain/discomfort that you experience can interfere with your daily activities and sleep. You use pain medication to manage your pain. **Sometimes your pain medication does not control your pain**.
- You occasionally feel anxious or depressed. **You worry about how your condition will progress in the future**.
- You feel self-conscious about your condition and sometimes experience bullying. You sometimes find it difficult to communicate your condition to others.
- You sometimes need help looking after yourself.
- You have some problems with understanding, memory, learning and attention. You may require additional help at school/work as well as support with developing and maintaining friendships.

Description S5

- You have a life-long genetic condition that causes lumps to grow in any part of the body, causing a range of symptoms. You have one main, large lump with an irregular shape.
- You receive **an oral medication twice a day** for your main, large lump. Your condition is monitored by your care team and you receive supportive care to help manage some of your symptoms.
- With treatment your condition is **improving**.
- **Your treatment occasionally causes you to have skin rashes**.
- The way you look is affected by your large lump. **Since you started treatment, you have noticed slight improvements in the size and appearance of your lump**.
- You have some difficulties with movement, strength and coordination. **Since you started treatment, you are able to move the area around your large lump slightly more freely**.
- You **sometimes** experience pain/discomfort in the area around your large lump. The pain/discomfort that you experience can interfere with your daily activities and sleep. You use pain medication to manage your pain.
- You occasionally feel anxious or depressed. **You are, however, enjoying life and feel optimistic about the future**.
- You feel self-conscious about your condition and sometimes experience bullying. You sometimes find it difficult to communicate your condition to others.
- You sometimes need help looking after yourself. **Since your condition has stabilised, you have needed less help with your daily activities**.
- You have some problems with understanding, memory, learning and attention. You may require additional help at school/work as well as support with developing and maintaining friendships.

Based on TTO document provided in response to request for clarification[81]
TTO = time trade off

TTO valuation exercise

Members of the general public were recruited by the interviewers through (online) advertisements, informal and online social networks and/or snowballing.[81] The study aimed to recruit 100 members of the general public to take part in the TTO interviews. All interviews were conducted by trained TTO interviewers. Interviewers were set quotas to ensure the sample is representative of the UK population in terms of age, sex, and ethnicity.

The TTO valuations ask participants to choose between two hypothetical lives: 10 years in a health state described by a vignette or X (10 or less) years in full health. Time X is varied until patients are indifferent between the two choices. If a participant is willing to trade all 10 years, this signifies that they may consider this state worse than dead. In this case a lead-time TTO exercise, which asks participants whether they would prefer to live for 10 years in full health followed by 10 years in a health state, or to live for 20 years of full health is provided to examine how much worse than dead the state is considered. TTO interviews were conducted online. A warmup exercise where participants were asked to rank two practice vignettes and death on the visual analogue scale was conducted before participants completed the TTO exercises for all vignettes. The resulting TTO utility values for each vignette are presented in Table 5.7.

Table 5.7: Utility values estimated for each vignette

PN location	Utility value off-treatment	Utility value on-treatment	Implied treatment effect
Unspecified (base-case)	[redacted]	[redacted]	[redacted]
Face	[redacted]	[redacted]	[redacted]
Trunk	[redacted]	[redacted]	[redacted]
Leg	[redacted]	[redacted]	[redacted]

Based on Table 23 of the clarification response,[53] and Table 4 of the TTO Study summary provided in Appendix 1 of the response to request for clarification[81]
PN = plexiform neuroma; TTO = time trade off

ERG comment: The ERG agrees that there are limitations associated with the HRQoL data collected. The EQ-5D is the preferred measure by NICE in general. However, this is a paediatric population, for which the standard EQ-5D is not considered most appropriate. There is a youth version of the EQ-5D, called EQ-5D-Y, but NICE have made no explicit statement of preference for how youth HRQoL must be measured and valued in appraisals.

PedsQL is a widely used measure of youth HRQoL for which a value set is available for the estimation of utilities. The ERG considers that this PedsQL data could have been used in a variety of ways, at minimum as a validation for the utilities produced by the vignette study. Baseline data were available which could have provided a utility estimate for standard of care, while other on-treatment measurements could have provided an estimate for the on-selumetinib state.

The argument that on-treatment follow-up was only 3 years could be considered a limitation, however, the way utility is currently modelled using the vignette utility values, there is no progression over time of utility within the model anyway (aside from usual general population decline due to ageing) and therefore this limitation does not represent a worse option than already modelled.

At clarification the ERG requested that the company perform a mapping analysis of the PedsQL to the EQ-5D using one of the available mapping algorithms.[57] The company declined stating that the only mapping function they were aware of is from a study by Khan et al. 2014,[83] which has been criticised for a variety of reasons.[53] Data were only collected in a relatively healthy sample of school children aged 11 to 15 years, limiting the applicability of the sample to broader ages and health states. SPRINT included children from 3 to 18 years of age.[53] The PedsQL includes age-specific forms, and six different versions covering different age groups and responders were used in the SPRINT trial: children (8 to 12 years of age), teenagers (13 to 18 years of age), parents reporting for children (8 to 12 years of age), parents reporting for teenagers (13 to 18 years of age), parents reporting for toddlers (2 to 4 years of age), parents reporting for young children (5 to 7 years of age).[53]

Therefore, the company concluded that mapping was inappropriate as it would not appropriately reflect the utility score of NF1 PN patients in the wider age range (3 to 18 years of age) from the SPRINT trial. They also stated that any improvements in HRQoL over the study period can also be confirmed through PedsQL scores themselves without the need of applying mapping algorithms. However, the ERG has no way of understanding how raw score differences on the PedsQL translate into differences in utility so nothing can be said about the appropriateness of the size of the difference in utilities observed in the vignette study using the PedsQL data presented.

The company considered that utility scores from the vignette study can be considered a better option for the modelling than mapping from PedsQL, as they reflect the preference of the general public regarding the NF1 PN specific health status. While the ERG agree that the vignette utilities represent the preferences of the general public as the TTO valuation was conducted in a representative sample of the general public, they fail to meet a different vital element of the NICE reference case which states that HRQoL must be measured/reported in patients. No patient HRQoL data are actually used to produce utilities in vignette studies. Members of the general public are given descriptions of health states which are intended to reflect the health of patients in different states in the model, and these descriptions are valued directly. No patient data are involved and therefore one cannot be sure how reflective these descriptions or the utilities produced are of the patients in the trial.

A general issue with vignette studies is how accurately a member of the general population is able to imagine the health state of a patient based on a description. NF1 PN is a very rare condition which the general public is unlikely to have experience with. The vignette health states presented, centre on the impact of a large lump on various aspects of life. It is unlikely that members of the general public will have ever seen such a condition before, and it is difficult to know how they conceptualise such a lump and its hypothetical impact on their life. Given that this is the central concept of the health state, valuations will be dependent on this conceptualisation.

The vignettes presented contains ten attributes each. This is a large amount of information for patients to retain and consider in their valuation. This may encourage heuristic short-cuts, where participants focus on a select subset of the attributes without considering others. The vignettes presented in Appendix 1 show that certain phases in some of the attributes were bolded. The bolded elements tend to focus on negative elements on the untreated vignette and positive elements on the treated. This increases the likelihood that participants will focus on these phrases if taking heuristic shortcuts and ignore non-bolded text.[81]

Lastly, while the ERG was encouraged that the off-selumetinib vignettes were validated with patients and carers, the treated vignettes were not. This is because the company excluded any patients who had received selumetinib, binimetinib, cobimetinib, mirdametinib or trametinib from their interview sample.[1] It is unclear why this decision was taken, as it is just as important to validate the on-selumetinib

states as the off-treatment states, as the treatment effect implied by the HRQoL data depends on both values.

5.3.3.7.3 Carer disutility

The company and clinical experts consulted considered that the HRQoL of parents, families and carers would be impacted through emotional distress, social isolation, stress and disruption to usual activities.[1] Experts considered that the support required by NF1 PN patients would not be limited by age, and would continue into the patient's adulthood.[1] However, no direct estimates of disutility due to caring for a NF1 PN patient were identified in the SLR and no study was performed by the company. Therefore, the company made the following assumptions in their base-case analysis:

- Parents/carers experience the same relative HRQoL decrement as for patients (patient decrement [redacted]).
- Starting from a mean age of parents of 30.6 years at childbirth based on data of the Office for National Statistics (ONS),[84] a general population utility value is determined using the regression algorithm from Ara and Brazier 2010; this represents the maximum parent/carer utility of a patient receiving selumetinib. Parent age is tracked in the model and utilities are adjusted accordingly, each model cycle.[85]
- The relative mean difference in utility between the selumetinib and current clinical management patient cohorts is calculated. This is used to weight and calculate the parent/carer utilities in the BSC arm.
- The impact of caring is included until the patient reaches the age of 18 years after which, it is assumed that no further support from parents and carers are required. The company consider this a conservative approach.
- Each patient was assumed to have 1.4 parents/carers, to which the caring disutility was applied, as the average UK household size is 2.4.[86]

The company acknowledge the uncertainty in this approach and therefore tested these assumptions in a series of scenarios. An alternative utility decrement of 0.08 per parent/carer was identified, based on the mean of utility values reported in HST11 (voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations).[87] The company noted that while this decrement is not specific to NF1, it incorporates parent/carer utilities for a wide range of patient health states, therefore representing the overall impact on the parent/carer. Additional scenarios involved varying the carer disutility as a proportion of the disutility experienced by patients, e.g. assuming 50% or 75% impact on parents/carers. The duration of the carer disutility was also explored in scenarios limiting the duration until the patient reached the age of 24 years or carers reached the age of 64 years.[1]

ERG comment: The ERG considers that the assumption that the impact of caring would be equal to the relative impact of the disease on patients (impact on patients of moving from on-treatment to progressive is [redacted]) to be unjustified. There is no evidence to support this assumption, which is substantially higher than carer disutilities observed in the literature and other NICE appraisals.

In a recent review of NICE appraisals, carer disutilities were identified in 6 technology appraisals (TAs) and 4 highly specialised technologies (HSTs) evaluation in paediatric or combined paediatric/adult populations.[88] This review identified several disutilities associated with caring for children, including a disutility of 0.11 for parents of children with Duchenne Muscular Dystrophy (DMD) at a non-ambulatory stage and a disutility of 0.07 for carers of children with activity limitations. Non-ambulatory DMD patients are unable to walk and have substantial care needs, which would be expected to be greater than those associated with NF1 PN. This does not lend support for a carer disutility of approximately

[redacted] as applied in the company base-case. The ERG would argue that a disutility of 0.07 may be more appropriate. The ERG note that the company incorrectly reported this 0.07 disutility as 0.08 and conducted scenarios on this mis-reported value.

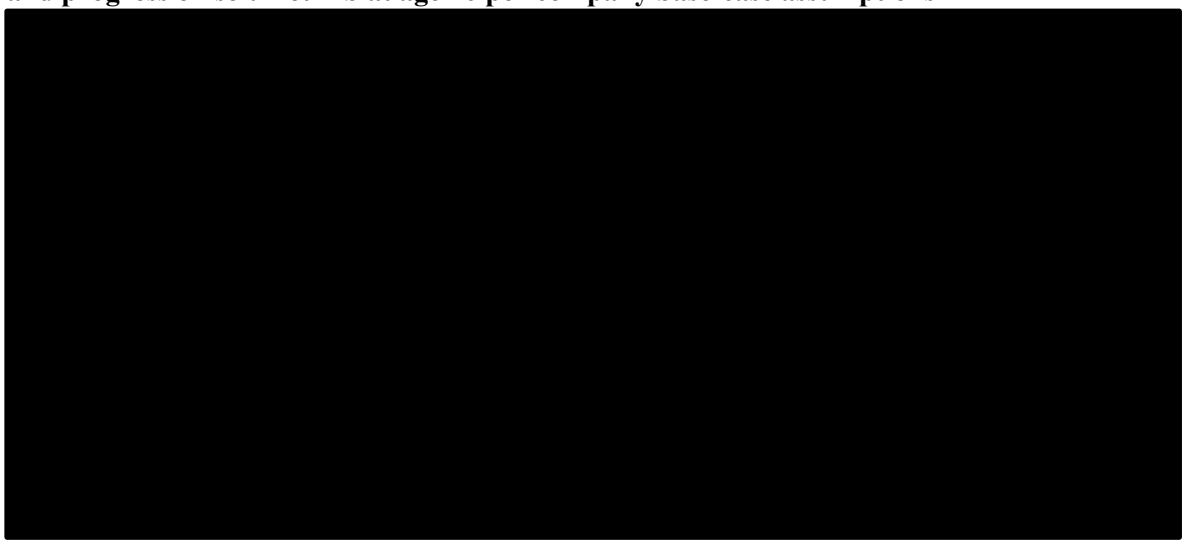
It is unclear how appropriate is the assumption that patients have an average of 1.4 carers, to which the full carer disutility is applied. This is simply based on the assumption that all members except the patient in an average UK household would be carers. However, this is a strong assumption as some households will include other children. The ERG considers that an assumption of 1 carer is more appropriate in the absence of any data relating to this population.

5.3.3.7.4 Modelling of HRQoL over time

In the BSC arm, patient HRQoL was assumed to remain constant over time at [redacted], as this was the value elicited for these patients in the vignette study. No further decrements due to events were incorporated. The benefit of selumetinib is modelled via improved utility values from baseline to [redacted] within 1 year (baseline utility assumed to be [redacted]). Utility remains constant for patients who maintain PR or stable disease. If a patient on selumetinib experiences substantial PN growth or progression (defined as a ≥20% increase in tumour volume from baseline, or if a patient had had a PR, an increase of at least 20% from the best response), their utility value declines downwards back to baseline, over a period of 5 years.[1]

The model assumes that PN volume stabilises once a patient reaches 18 years of age, in both the selumetinib and BSC arm.[53] Therefore, no additional progression events will occur after a patient reaches 18 years of age in the model. If a patient reaches 18 years of age during this 5-year waning period, their HRQoL is assumed to persist at the level reached for the rest of the model. The company stated that *"due to the preventative nature of initiating treatment with selumetinib and limiting PN growth in children, lifelong benefits are anticipated, as validated by several UK clinical experts who confirmed the importance of selumetinib in controlling tumour size into adulthood, whereby growth rates tend to plateau"*.[30] The impact of this assumption on utility is shown in Figure 5.6, which presents at example of the utility of a patient who experiences a progression event at age 16 years. Age-related decline in HRQoL was included in the model using the equation by Ara and Brazier.[85]

Figure 5.6: Utility over time for patients who receive: BSC only; remain stable on selumetinib and progress on selumetinib at age 16 per company base-case assumptions



Based on the economic model accompanying the CS[1]
BSC = best supportive care; CS = company submission

ERG comment: The lack of decline in utility over time (beyond the standard age-related decline) in the progressive state is not reflective of the reported progressive nature of NF1 PN. The company argue that this is a conservative assumption, as progression would occur earlier and more often in the BSC arm.

The company assumed a linear waning in treatment effect and therefore utility from [redacted] to [redacted] over 5 years after progression. No justification or supporting evidence for assuming a period of 5 years waning utility was provided. Given that patients are stated to discontinue treatment with selumetinib at age 18 years and that the model mean starting age is [redacted] years of age, this 5-year period represents a substantial additional period of benefit relative to the maximum treatment period of approximately [redacted] years. As shown in Figure 5.6 above, the impact of this assumed 5-year waning is increased by the accompanying assumption that utility remains stable after the age of 18 years, which allows for the modelling of a lifetime treatment effect for progression events occurring from the age of 14 years. The utility value for the progressed state is based on a vignette describing a large lump that is growing and a lack of treatment. This is already reflective of the health state at progression. Additionally, the company assumed that utility only took 1 year to linearly increases to the on-treatment utility value upon treatment initiation and no evidence of why the reverse process should take 5 years instead of one was presented. Therefore, the ERG prefers a waning of 1 year upon progression.

Another limitation of the model is that utility is not linked to discontinuation. Therefore, when patients discontinue treatment in the model, their utility remains the same. Only progression is assumed to impact utility. Changing the discontinuation rate or extrapolation model has no impact on QALYs. This is unrealistic, given that it is assumed that all patients not receiving treatment in the BSC arm will have progressive disease, which is associated with a much lower utility, but the same assumption is not applied in the selumetinib arm, which will bias results in favour of selumetinib. It is important to note that despite the company often referring to the vignettes and health state utility values presented as on- and off-treatment vignettes and utilities, in the model the utilities are treated as on-treatment and progressive utilities.

The ERG agrees with the inclusion of age-related decline in utility within the model. However, they note that this was modelled using the equation provided by Ara and Brazier.[85] This equation was estimated in adults but has been extrapolated to children of 10-17 years. It is unclear how appropriate these values are; however, the impact is likely to be small.

5.3.3.7.5 Impact of adverse events on HRQoL

Several AEs were included in the economic model, as discussed in Section 5.3.3.6 of this report. However, disutilities were not included in the model for these events.

ERG comment: The company note that the impact of dermatitis acneiform was included in the on-selumetinib health state vignette, so the impact of this AE should be reflected in the valuation.[53] Given the short duration for the other included AEs and the low incidences observed, it is unlikely that the exclusion of these AE disutilities has a large impact on results. However, for completeness these should have been included. Given that there was no implementation for AE disutilities to be easily added within the model, the ERG did not have time to make this change.

5.3.3.8 Resources and costs

The company's base-case analysis included the following health care resource use costs: drug acquisition costs for selumetinib, the treatment monitoring costs of two additional MRI scans for

patients receiving selumetinib, pain medication costs, and costs for the medication used in the management of treatment-related AEs.

5.3.3.8.1 Drug acquisition costs

Selumetinib is provided as 10 mg capsules in a pack size of 60 capsules at a list price of £4,223.59, and as 25 mg capsules in a pack size of 60 capsules at a list price of £10,560.00. A simple patient access scheme (PAS) discount of [redacted] has been submitted to NICE PAS Liaison Unit (PASLU), resulting in a discounted net price of £[redacted] for a pack of 10 mg capsules (60x) and £[redacted] for a pack of 25 mg capsules (60x). The price including PAS discount was used for the company's base-case analysis.

Selumetinib is administered at a dose of 25 mg/m^2 BSA, twice daily (approximately every 12 hours), up to a maximum single dose of 50 mg. Dosing assumptions were based on the same dosing nomogram as in SPRINT Phase II Stratum I, with doses rounded to the nearest 5 to 10 mg. This dosing nomogram, including the corresponding cost per dose, cost per day and cost per year, is provided in Table 5.8.

Table 5.8: Selumetinib dosing nomogram from SPRINT

BSA (m^2)	0.55 to 0.69	0.70 to 0.89	0.90 to 1.09	1.10 to 1.29	1.30 to 1.49	1.50 to 1.69	1.70 to 1.89	1.90 to 2.04
Dose required (25 mg/ m^2/ dose)	20 (morning) 10 (evening)	20	25	30	35	40	45	50
Capsules required to deliver dose								
10 mg	1.5	2	-	3	1	4	2	-
25 mg	-	-	1	-	1	-	1	2
Costs per dose, per day and per year (£)								
Cost per dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables D10 and D11 from the CS[1]
BSA = body surface area; CS = company submission

BSA was modelled based on data from SPRINT Phase II Stratum I. At baseline/model entry, patients had a mean BSA of [redacted], which is then assumed to increase annually according to a linear regression algorithm that was estimated based on age and gender split. The regression coefficients used for the linear estimation of BSA are provided in Table 5.9, and the linear regression results plotted against the observed SPRINT data are provided in Figure 5.7. BSA is assumed to stabilise from the age of 18 years, when patients are also assumed to discontinue treatment. The model also provides the option to use only the linear regression to estimate BSA at model entry, i.e. not using the baseline BSA from SPRINT, based on age at baseline/model entry. When this option is used, the ICER is increased from £93,169 to £101,613 per QALY gained.

Table 5.9: BSA linear regression parameters

Parameter	Value

Age	[redacted]
Constant	[redacted]
Based on Table D12 from the CS[1] BSA = body surface area; CS = company submission	

Figure 5.7: Fit of linear regression to BSA data over time from SPRINT

Based on Figure D5 from the response to request for clarification[53]
Note: The figure presented in the CS was incorrect
BSA = body surface area; CS = company submission

5.3.3.8.2 Treatment monitoring costs

For the monitoring of patients receiving treatment with selumetinib, two additional outpatient MRI scans are included at a cost of £264.50 per MRI examination that was sourced from the NHS Reference costs 2018/2019 [Currency description: Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning; Currency code: RD07Z].[89]

5.3.3.8.3 Pain medication costs

The costs of pain medication were included based on a weighted average of all concomitant pain medication that was used during the treatment period in SPRINT Phase II Stratum I safety analysis set (SAS; n=50) and applied annually. A weighted average cost for pain medication per patient per year of £[redacted] was calculated using the pain medications, and corresponding assumptions on dosage, costs that were sourced from the British National Formulary (BNF), and proportions and numbers of patients that used each medication as provided in Table 5.10.

Table 5.10: All concomitant pain medication used during the treatment period in SPRINT Phase II Stratum I Safety Analysis Set

Pain medication	Dose	Pack size	Price (£)	£/unit	£ p.a.	% of pts	N
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pain medication	Dose	Pack size	Price (£)	£/unit	£ p.a.	% of pts	N
[redacted]							

Based on the electronic model provided by the company in their response to the request for clarification[53]
[a] Assumed to have been used as cream formulation; [b] Assumed to have been used as sublingual formulation; [c] The company indicated in the model that it was assumed that fentanyl is for short term use and the proportion (4%) /number (2) of patients that used this were set to zero; [d] The company indicated in the model that it was assumed that ketamine was only used in a hospital setting and no costs were applied.

The company assumed that the use of pain medication in patients receiving BSC was increased relative to the use in patients receiving selumetinib by [redacted]%. The company indicated that this assumption was based on findings by Gross et al. 2018,[7] who observed that the use of pain medication increased by [redacted]% over the course of a natural history study on patients with NF1 PN. As such, for patients receiving BSC the cost of pain medication was assumed to be £[redacted].

5.3.3.8.4 Adverse event costs

For the most common Grade ≥3 AEs as observed in SPRINT the costs for the management of AEs associated with selumetinib were included, with appropriate treatments selected based on local clinical feedback, and sourced from the BNF. The included AEs, the costs of their treatment, and weighted average cost are provided in Table 5.11. The weighted average cost for treatment of AEs was applied annually.

Table 5.11: Costs of adverse events with selumetinib

Adverse event	Treatment	Estimated cost per event (£)	Proportion of patients experience AE
Diarrhoea	Loperamide (various doses – assumed a single pack would resolve symptoms. 2mg, 30 tablets at £1.58 per pack)	1.84	[redacted]
Vomiting	Ondansetron (4mg, two times per day for up to 5 days– 10 tablets at £1.07 per pack)	1.07	[redacted]
Pyrexia (Fever)	N/A	N/A	[redacted]
Hypoxia	N/A	N/A	[redacted]
Paronychia	Flucloxacillin (250 mg four times a day for 7 days – 28 caps at £1.72 per pack)	37.71	[redacted]
Dermatitis acneiform	Metronidazole cream (Typical duration of symptoms was 4 months, assume one 40 mg unit would be sufficient for 1 month treatment. 40g of, 7.5 mg metronidazole per gram, at £9.88 per unit)	3.44	[redacted]
Weighted average cost	-	[redacted]	

Based on Table D13 of the CS[1]
AE = adverse event; CS = company submission; N/A = not applicable.

ERG comment: The company's base-case analysis only included the following health care resource use costs: drug acquisition costs for selumetinib, the costs of two additional MRI scans for patients receiving selumetinib, pain medication costs, and costs for the medication used in the management of treatment-related AEs.

Clinical expert opinion consulted by the company indicated that the following, additional types of health care resource use are or may be relevant to consider for patients with symptomatic, inoperable NF1 PN: clinical nurse specialist support, educational support, physiotherapy, psychological support, occupational therapy, clinical appointments for the follow-up and monitoring of treatment with selumetinib, and the use of medication for anxiety and depression in adult patients.[30]

During the clarification phase, the ERG requested the company to explain whether all relevant costs in relation to general disease management and monitoring had been included, and if not, to include all relevant costs.[57] The company responded by confirming that only a limited number of cost items was included due to the heterogeneity in patient management and symptomatic management and that they considered this to be a conservative approach.[53]

Furthermore, the company indicated that the analysis assumed that all health care resource use costs in relation to general disease management and monitoring will be the same in both arms and therefore cancel each other out. The company also indicated that due to its effect on PN volume patients treated with selumetinib may require fewer visits to manage their disease and symptoms. However, the company indicated that there is no specific data to support a quantitative difference in the symptom management costs other than pain medication costs and that it was decided to exclude the majority of these costs for simplicity and to avoid unnecessary uncertainty.

In addition, the company indicated that experts noted that selumetinib may require additional monitoring to determine treatment efficacy (tumour volume reduction/ stabilization) and potential side effects and may reduce the need for pain medication. The additional monitoring requirements were accounted for by including the costs of two additional MRI scans per year for patients that are treated with selumetinib. The company indicated that costs for the management of PN-associated morbidities were also excluded from the analysis due to heterogeneity in this aspect. According to the company this was a conservative assumption, since they anticipated that a reduction in PN volume, i.e. from treatment with selumetinib, would lead to reduced PN-associated morbidity costs. In addition, the company indicated that there are no means to quantify this aspect with the only exception being pain medication costs that were included in the analysis.

According to the ERG, the limited number of cost items that the company included in their base-case analysis does not provide a representative overview of all relevant costs in relation to general disease management and monitoring. For example, in a study by Yang et al. 2020 on resource use and costs in patients with NF1 PN in the United States,[90] which was identified by the company through a systematic literature search on relevant resource data, it was found that 99.7% of patients had outpatient visits, 81.1% had pharmacy visits, 25.2% had emergency room visits, 13% had inpatient visits, 44.2% used pain medication, 23.9% received chemotherapy, 5% underwent surgery, 1.3% received radiotherapy and 1.0% received targeted therapies. From this it is clear that the limited number of cost items that were included do not provide a comprehensive overview of all items that are potentially relevant. As such, this is an important source of uncertainty.

However, the ERG agrees that the inclusion of additional cost items would require data on the resource use in patients treated with selumetinib which does not seem to be currently available. Also, the ERG considers it plausible that any relevant disease management costs, i.e. other than costs in relation to the additional monitoring requirements or management of treatment-related AEs that are specific for treatment with selumetinib, will be reduced following treatment with selumetinib. Therefore, the ERG agrees that the simplification to exclude these costs may be seen as a reason to interpret the cost-effectiveness results as conservative estimates.

The ERG considers the calculation of the drug acquisition costs based on BSA, implemented using the BSA at baseline from SPRINT in combination with an annual increase as estimated by linear regression, as appropriate. However, given the impact on the ICER when using the option to use BSA as estimated only using the linear regression based on age at baseline, the ERG has performed a scenario analysis where this option is used with the ERG preferred version of the model (see Section 6.4.4 of this report).

For the additional monitoring requirements that are specific to treatment with selumetinib, the company assumed the costs of two MRI scans per year. This frequency was assumed based on the minimal number that was indicated by the clinical experts consulted by the company. Based on the information in Table 10 of the documentation on clinical expert opinion that was provided to the ERG, only one out of four clinical experts reported their estimate of additional monitoring requirements quantitively. This expert estimated that additional monitoring would occur once per month initially and once per every three months thereafter. As such, the ERG considered the inclusion of additional MRI scans at a frequency of twice per year too low. For the ERG preferred base-case analysis it was assumed that additional MRI scans are required at a frequency of four times per year. When applied in isolation of the other ERG changes, this increased the ICER from £93,169 per QALY gained to £93,515 per QALY gained.

In contrast to the data on pain medication use (as provided in the economic model, Sheet: painMedications), [redacted]. Another deviation from the data, presumably an error, was that [redacted]. To account for differences in the use of pain medication between patients treated with selumetinib versus BSC, the company assumed an increase of [redacted]% in pain medication costs for BSC relative to selumetinib. This number was based on a study by Gross et al. 2018,[7] who, according to the company, found that 67.5% of PN required increasing pain medication during the observation period. The ERG could not reproduce this value from Gross et al. 2018.[7]

In addition, the ERG notes that an increase in the proportion of PN requiring pain medication is not the same as an increase in costs for pain medication. However, based on the results of a scenario analysis where the costs of pain medication and AEs were excluded, decreasing the ICER from £93,169 to £92,821 per QALY gained, the company concluded that these costs only had a minimal impact on the cost effectiveness results. Therefore, the ERG did not make any changes to the assumptions on pain medication costs for the ERG preferred base-case analysis.

5.3.4 Model evaluation

The health economic analyses results are presented in terms of the incremental QALYs and incremental costs for selumetinib compared to BSC. The CS also included the results of one-way deterministic sensitivity analyses and a probabilistic sensitivity analysis (PSA). In the deterministic one-way sensitivity analysis parameters were varied one by one using the upper and lower bounds of 95% CIs, where available, or 20% deviation from their mean values otherwise. The ICER was recorded for each upper and lower bound, and the 10 parameters with the largest impact on the ICER were presented in a tornado diagram. In the PSA, probability distributions were assigned to the model input parameters to assess the uncertainty around all parameters simultaneously. Where standard errors were not available, these were estimated using the formula (upper bound – lower bound)/(2*NORMSINV(0.975)), where the NORMSINV function returns the inverse of the standard normal cumulative distribution in Microsoft Excel. The upper and lower bounds were based on 95% CIs, where available, or assuming 20% deviation from the mean value otherwise. The PSA was conducted using 10,000 simulations. Results were recorded in the form of incremental costs and incremental QALYs and were plotted on a cost-effectiveness plane. A cost effectiveness acceptability curve (CEAC) was estimated from the results of the PSA. A list of the parameters and their corresponding probability distributions included in the PSA are shown in Table 5.12. Finally, several scenario analyses were also explored by the company to assess the impact of varying modelling assumptions on the cost effectiveness results.

Table 5.12: Parameters included in the one-way and probabilistic sensitivity analysis

Parameter	Base-case value	Range	Probability distribution
Proportion of males	[redacted]	[redacted]	Beta
Average age at entry	[redacted]	[redacted]	Gamma
BSA at entry	[redacted]	[redacted]	Gamma
NF1 SMR	2.02	1.6 to 2.6	Gamma
Weibull: shape parameter	[redacted]	[redacted]	Cholesky

Parameter	Base-case value	Range	Probability distribution
Weibull: scale parameter	[redacted]	[redacted]	Cholesky
Utility: with selumetinib	[redacted]	[redacted]	Beta
Utility: without selumetinib	[redacted]	[redacted]	Beta
Utility: age adjustment constant	0.951	0.761 to 1.141	Gamma
Utility: age adjustment male coefficient	0.021	0.017 to 0.025	Beta
Utility: age adjustment age coefficient	-0.00026	-0.00021 to -0.00031	Normal
Utility: age adjustment age^2 coefficient	-0.00003	-0.000027 to -0.000040	Normal
Discount rate: outcomes	3.50%	1.50 to 6.00%	N/A
Discount rate: costs	3.50%	1.50 to 6.00%	N/A
Cumulative probability of progression by Year 3	16.00%	5.84 to 26.16%	Beta
BSA: linear regression constant	[redacted]	[redacted]	Beta
BSA: linear regression coefficient for age	[redacted]	[redacted]	Beta
Number of carers	1.4	0 to 2	Gamma
Parents age at birth of patient	30.6	20 to 40	Gamma
Years to revert to untreated HRQoL	5	2 to 8	Gamma
Cost of MRI	£265	£60 to £301	Gamma
Annual number of MRIs for selumetinib patients	2	0 to 4	Gamma
Cost of managing selumetinib AEs	[redacted]	[redacted]	Gamma
Cost of pain medication for patients receiving selumetinib	[redacted]	[redacted]	Gamma
Increase in pain medication for those on BSC	[redacted]	54 to 81%	Beta

Based on Table D15 of the CS[1]
AE = adverse event; BSA = body surface area; BSC = best supportive care; CS = company submission; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; N/A = not applicable; NF1 = type 1 neurofibromatosis; SMR = standardised mortality ratio

5.4 Headline results reported within the company's submission

This section summarises the results of the economic analyses as presented by the company in the CS and, when relevant, in the response to the clarification letter.[53]

5.4.1 Deterministic results of the company (base-case)

The company base-case results are summarised in Table 5.13 using the approved PAS price for selumetinib. Selumetinib accrued [redacted] incremental QALYs compared to BSC at an additional cost of [redacted]. This corresponds to an ICER of £93,169 per QALY gained.

Table 5.13: Company base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	93,169

Based on Table D16 of the CS[1]
BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

5.4.2 Sensitivity analyses presented within the company's submission

The company conducted a number of sensitivity and scenario analyses. The results of these analyses are summarised in the remaining of this section. Only discounted results are discussed here.

5.4.2.1 Sensitivity analyses

The results of the deterministic one-way sensitivity analysis (OWSA) for selumetinib versus BSC are presented in the form of a tornado diagram in Figure 5.8, showing the 10 parameters with the largest impact on the ICER. The results were most sensitive to changes in input parameters related to treatment duration, health states utility values (HSUV), discount rates, parent, and carer HRQoL assumptions and probability of progression.

Figure 5.8: One-way sensitivity analysis - ICER results

[redacted]

Based on Figure D8 of the CS[1]
BSA = body surface area; CS = company submission; ICER = incremental cost effectiveness ratio

5.4.2.2 Probabilistic sensitivity analyses

A PSA was conducted using 10,000 Monte Carlo simulations. Average results are in line with the deterministic base-case and can be seen in Table 5.14. Individual PSA simulations were plotted in the cost effectiveness (CE) plane shown in Figure 5.9. [redacted]. A

CEAC was derived and shown in Figure 5.10. At the threshold ICER of £100,000 per QALY gained, the probability that selumetinib is cost effective compared to BSC is [redacted]%.

Table 5.14: Company probabilistic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	90,741

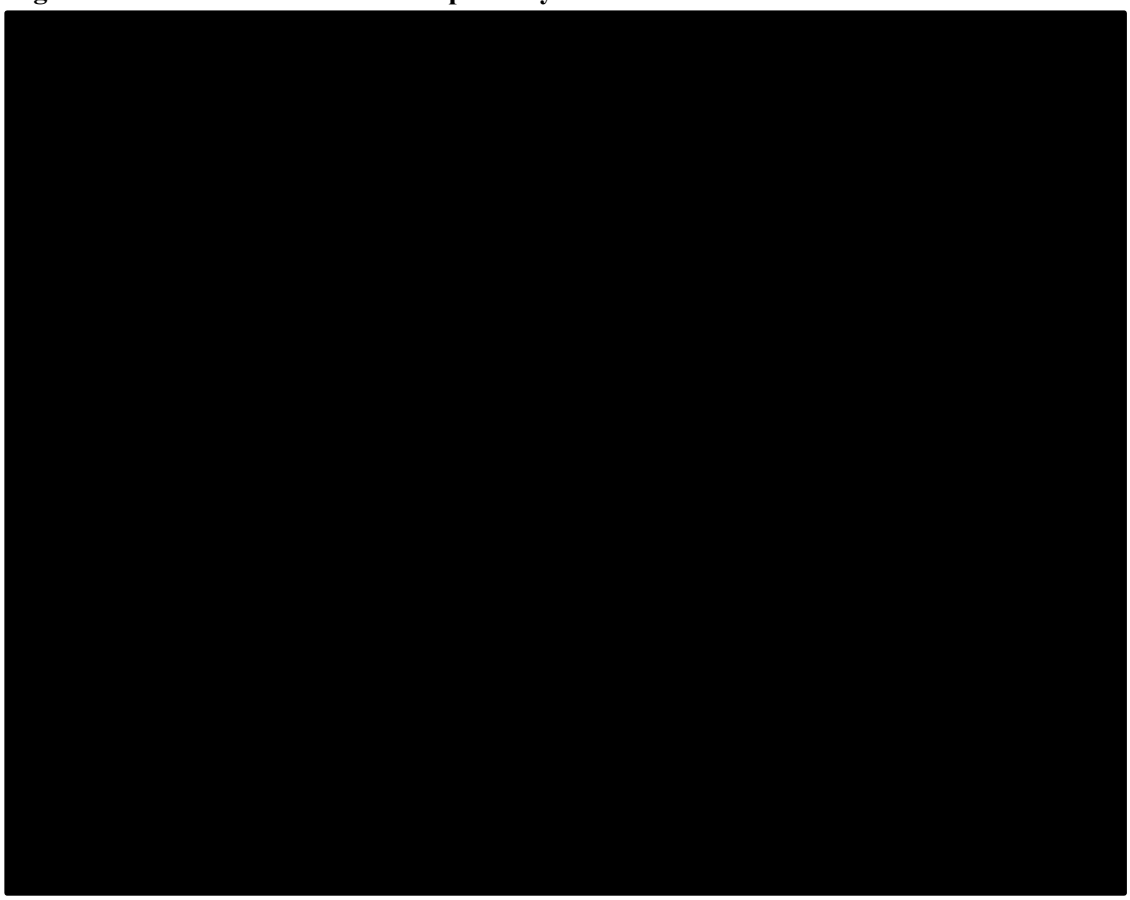
Based on Table D20 of the CS[1]
BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; NR = not reported; QALY = quality-adjusted life year

Figure 5.9: Probabilistic sensitivity analysis scatterplot company base-case

[redacted]

Based on Figure D9 of the CS[1]
CS = company submission; QALY = quality-adjusted life-year

Figure 5.10: Cost effectiveness acceptability curve



Based on Figure D10 of the CS[1]
BSC = best supportive care; CS = company submission

ERG comment: The ERG identified some issues regarding the PSA:

- The button to run the PSA in the "_Parameters" worksheet gives an error unless some of the model worksheets become unhidden.
- Once unhiding the worksheets, the PSA macro seemed to reset all values back to the company base-case.
- To run the ERG PSA, the ERG inputted manually the values changed for their base-case in "_Parameters" column G.
- The coefficients in the age-dependent utility decrements and BSA equations are sampled independently in the PSA, which might lead to inconsistent values being drawn for some PSA iterations. The ERG could not correct this, but it is expected to have a minor impact on the results.
- In response to clarification question B18, the company indicated that for some parameters, standard deviations instead of standard errors were used in the PSA.[53] The company explained that due to the high uncertainty in many model parameters, this is unlikely to significantly influence the PSA. The ERG, however, cannot judge this because it is not explained for how many parameters this happened.

5.4.2.3 Scenario analyses

Several scenario analyses were conducted by the company in order to explore the impact of varying the model assumptions on the model results. The scenarios explored are described below and their results summarised in Table 5.15.

5.2.4.3.1 Patient age at the beginning of the simulation

Patient age is used to estimate BSA which is used to calculate the cost of selumetinib. The company indicated that UK clinical experts supported the base-case assumption of an average starting age of [redacted] years in the SPRINT study based on the following reasons:[30]

- SPRINT data were deemed generalisable to the UK setting.
- Starting treatment very early is unlikely to occur in clinical practice due to multiple practical reasons, including the likely inability to swallow capsules at a young age (<7 years) and the time needed for PN to develop to become symptomatic (and to be deemed inoperable)
- One expert suggested these reasons could lead to starting treatment after 10 years of age (perhaps in early adolescence).

However, selumetinib is indicated in paediatric patients with symptomatic inoperable NF1 PN, who may start treatment from 3 years old. It is unclear what the average age of treatment initiation would be in clinical practice. The scenarios explored assumed patients would start treatment at 5 years and 15 years of age, respectively. A scenario assuming 7 years was presented in the response to the request for clarification.[53] The ICER increased with age as expected. However, in response to clarification question B15, the company explained that in order to run a scenario with a different age, BSA calculated from linear regression (instead of directly estimated from SPRINT) has to be selected.[53]

It should be noted that selecting BSA calculated from linear regression changes the ICER even if age is not changed. For example, in the company base-case (age is 10 years), the ICER would increase to £101.613 when this option is selected. Therefore, the differences in ICER are not completely attributable to the change in age but also to the way BSA is implemented in the model. Also, in the model there is no link between age and PFS. Thus, the model applies the same PFS independently of age, which seems to be in contradiction with the evidence presented in the CS. Age should also be linked to other model parameters like the age of the caregivers/parents, but this is not done in the model (it can be done manually), even though this change in particular has almost no impact on the results. Hence, the results from these scenario analyses should be interpreted with caution.

5.2.4.3.2 Alternative parametric distributions for TTD

Several parametric distributions for TTD extrapolation were explored. The company argued that similar AIC and BIC values were found across all distributions, whilst the Weibull distribution was the most clinically plausible and, therefore, chosen for the base-case. All scenarios resulted in ICERs higher than in the base-case analysis. Note, however, that in the model TTD only impacts total costs but not QALYs since TTD is not linked to PFS or HRQoL. Therefore, the results from these scenario analyses should also be interpreted with caution.

5.2.4.3.3 Alternative discount rates

According to the NICE Guide to the Methods of Technology Appraisal, a non-reference case discount rate of 1.5% for costs and outcomes may be considered if it is highly likely that long-term health benefits will be achieved.[79] The company argued that HRQoL benefits are likely to persist for the patients' lifetime given that PN progression slows or is not present in adulthood. The impact of discounting results by 1.5% decreased the ICER by more than £20,000 per QALY gained.

5.2.4.3.4 Excluding treatment-related costs for selumetinib (AEs, MRI scans)

The company run a scenario where additional treatment-related costs of AEs and MRIs associated with selumetinib were excluded from the analysis. This had a minor impact on the model results.

5.2.4.3.5 Alternative assumptions regarding SMR Exclusion of SMR

The company conducted two scenarios in which alternative assumptions on the SMR were explored. The first scenario excluded the SMR rate associated with NF1 from the analysis, which had a minimal impact on the results. The second scenario assumed an additional benefit of selumetinib on patient mortality, since reduced and stabilised PN volume may correspondingly reduce the risk of malignancies such as MPNSTs. Given the lack of data to inform this assumption, an arbitrary improvement of 5% was assumed, resulting in an SMR of 1.92 compared to the baseline ratio of 2.02 for BSC patients. Changing this assumption had also a minimal impact on the results. To assess the uncertainty regarding alternative assumptions on excess mortality, the ERG would have preferred the use of the upper and lower bounds of the 95% CI for the estimated SMR rather than the arbitrary improvement of 5% that the company assumed. However, given the small impact of alternative assumptions for this parameter on the results the ERG has not performed any additional scenario analyses.

5.2.4.3.6 Parent/carer utility (relative difference)

Several analyses were conducted to explore the impact of different assumptions of parent and carer HRQoL on the model results. These included the size of impact on parent/carer HRQoL relative to the benefit experienced patients, the duration of burden on parents/carers, and an alternative approach using a single disutility value obtained from a previous HST submission. The ICER was sensitive to changes on parent/carer utility assumptions with ICERs ranging between £66,314 and £115,483.

5.2.4.3.7 Alternative assumptions on utility change over time

Finally, the company explored four scenarios in which assumptions on the health state utilities were changed. In the base-case analysis it was assumed that patients on BSC start with the utility of an untreated patient ([redacted]) and patients receiving selumetinib are associated with the utility of a treated patient ([redacted]) over the first year. In these scenarios the company assessed the impact of different assumptions regarding the HRQoL benefits associated with selumetinib on the model results, by varying:

- how quickly patients are assumed to experience the HRQoL benefit from the start of treatment; and
- the duration of sustained benefits after discontinuation.

According to the company, data from SPRINT demonstrate a rapid improvement in HRQoL after treatment initiation, a durable response, and improvements in clinical outcomes. Adding to these observed effects the clinical rationale underlying the lifelong benefit of preventing and limiting the impact of PN in childhood, led to the company to deem these scenarios as conservative. However, one of the scenarios resulted in a lower ICER than in the base-case.

5.2.4.3.8 Progression-free survival

As shown in the tornado diagram in Figure 5.8, PFS was included in in the one-way deterministic sensitivity analysis. This analysis considered a CI of [redacted]% to [redacted]% for the cumulative probability of progression by year 3 (base-case was [redacted]%). At the lower bound the ICER decreased to £76,065 per QALY gained and increased to £115,883 per QALY gained at the upper bound. Note that these scenarios only led to changes in QALYs but not in costs. This is because in the model there are no costs associated to being in the PFS health state.

Table 5.15: Scenario analyses results

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£)
Base-case	Section 5.3 of this report	[redacted]	[redacted]	93,169
Starting age*	5 years	[redacted]	[redacted]	72,721
	7 years	[redacted]	[redacted]	84,637
	15 years	[redacted]	[redacted]	133,797
Alternative parametric distributions for TTD	Exponential	[redacted]	[redacted]	100,087
	Generalised gamma	[redacted]	[redacted]	102,307
	Gompertz	[redacted]	[redacted]	94,922
	Loglogistic	[redacted]	[redacted]	100,178
	Lognormal	[redacted]	[redacted]	105,027
Alternative discount rates	1.5% for costs and outcomes	[redacted]	[redacted]	70,553
Treatment-related costs	No selumetinib treatment-related costs	[redacted]	[redacted]	92,821
SMR	No SMR assumed	[redacted]	[redacted]	91,390
	Differential SMR	[redacted]	[redacted]	93,659
Parent/carer utility	Relative difference 75%	[redacted]	[redacted]	100,615
	Relative difference 50%	[redacted]	[redacted]	109,355
	Impact until patient reaches 24 years	[redacted]	[redacted]	82,463
	Impact until parent/carer reaches 64 years	[redacted]	[redacted]	73,410
	Impact for duration parent/carer lifetime	[redacted]	[redacted]	66,314
	Absolute utility decrement 0.08 in BSC	[redacted]	[redacted]	115,483
Utility change over time	Years to achieve treated HRQoL after initiating treatment: 2 years	[redacted]	[redacted]	96,923

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£)
	Years to achieve treated HRQoL after initiating treatment:3 years	[redacted]	[redacted]	101,377
	Years to revert to baseline HRQoL after discontinuing treatment (2 years)	[redacted]	[redacted]	99,762
	Years to revert to baseline HRQoL after discontinuing treatment (3 years)	[redacted]	[redacted]	87,740
Progression-free survival	Cumulative probability of progression by year 3 = [redacted]%	[redacted]	[redacted]	76,065
	Cumulative probability of progression by year 3 = [redacted]%	[redacted]	[redacted]	115,879

Based on Tables D21 to D35 of the CS as well as Tables 30 and 32 in the response to the request for clarification[53]

* Correct results in response to the clarification letter

BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; NR = not reported; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TTD = time to discontinuation

5.4.3 Validation

The company indicated very briefly in Section 12.7 of the CS that the model has been quality checked by a senior health economic modeller that was not involved in the model development. Quality assurance entailed reviewing modelling structural assumption, techniques chosen, technical deployment (formulas, functionality) and data inputs and sources. Additionally, extreme scenario analyses were conducted, and validation of results was assessed. However, no further details were provided and with the information in the CS, the ERG cannot assess whether the model has been properly validated or not. In response to question B18 of the request for clarification,[53] the company submitted a completed version of the TECH-VER checklist.[91] This led to the identification of a couple of minor errors that had no impact on the base-case.

Also, in response to question B18 of the request for clarification the company explained that for the initial clinical validation of the model, methods and assumption were presented to four European clinical experts, including one clinician from the UK.[53] Experts were presented with the model structure, residual benefit post discontinuation, key cost, utility and clinical assumptions (including use of parametric models fitted to TTD). All clinicians felt that data used, and the pragmatic assumptions were reasonable. As a result of this initial validation, the additional costs for MRI scans were included in the model.

At a later stage, a second validation round was carried out to ensure that the modelling was appropriate and applicable to the UK setting (see Section 10.6.2 of the CS).[1] The company consulted four clinical experts, with 1-hour teleconferences, carried out in July 2021.[2] The experts (two paediatric oncologists, one lead nurse, and one geneticist) are currently involved in the management of paediatric NF1 patients. The latter two experts are also involved in 'lifespan' service and see both children and adults with NF1 PN. The experts were selected on the basis that they were all based in England and had direct experience treating patients with NF1 PN. Furthermore, all experts had direct experience of selumetinib use in their centre. Feedback was obtained via structured interviews including questions on the following topics:

- Clinical course of symptomatic inoperable NF1 PN and the current clinical pathway for patients
- Comparability of the SPRINT study population with UK setting
- Clinical benefit of selumetinib and any safety/tolerability considerations
- Wider aspects of care for patients, parents, and carers
- The link between the disease course of NF1 PN and HRQoL over time, and the potential impact selumetinib as incorporated in the economic model

From the UK validation exercise general consensus was agreed upon the following:

- Under current clinical management without selumetinib, the HRQoL of patients with NF1 PN is low for both children and adults
- The HRQoL of patients treated with selumetinib will be higher than those receiving only current clinical management
- Some patients receiving selumetinib will experience reduced or stabilised PN growth. This results in an optimal/peak HRQoL value
- Some patients receiving selumetinib could still experience disease progression at some point. This would have a negative impact on HRQoL
- There are reasons to believe that selumetinib could continue to benefit patients after treatment discontinuation, i.e., the benefit of starting treatment in the paediatric setting is preventative in

nature, and that the intention would be to intervene to limit the impact of NF1 PN on the patient as early as possible

- Selumetinib will form an effective preventative therapy for patients whose PN would otherwise grow and persist into adulthood, with associated disease burden

ERG comment: It seems that the company has taken the necessary steps to ensure the validity of the computerised model (model verification) and that the conceptual model was validated with clinical experts. This was not surprising given the rarity of the disease and lack of previous model for this disease.

However, as discussed in Section 5.3.2, the heterogeneity of the disease and the association between treatment effect and age, PN volume or number of PN-related morbidities are not captured by the current model.

Furthermore, with the current model structure, the evidence provided in the CS supports the assumption that PFS should also be in the comparator arm of the model, which in the end was not included in the model. The ERG wonders whether these aspects were discussed with the experts and what their feedback was.

The assessment of the validity of the input data is missing from the CS too. The main ERG concerns regarding the input data used in the model are related to the modelling of PFS (as discussed in Section 5.3.3.3) and the external validity of the HSUV estimated from the vignette TTO study (as discussed in Section 5.3.3.7). Finally, the assessment of the operational validity of the model (i.e. the validity of the model outcomes) appears to be limited, especially with regards to cross-validation testing and validation against empirical data. It is clear that cross-validation testing could not be assessed given the lack of similar models for which outcomes could be compared with. There was also no attempt to try to validate the model outcomes against empirical data. While the ERG understands the data are limited, especially for the selumetinib arm, model outcomes could have been compared for example with SPRINT data or with available data describing the natural disease progression, i.e. the BSC arm.

5.5 Discussion of the available evidence relating to value for money for the NHS and PSS

Progressive PN growth is associated with an increase in the number and severity of morbidities over time, resulting in a corresponding decrease in HRQoL. However, number and severity of morbidities are not included in the model. The evidence provided in the CS also suggests that disease progression strongly varies with age, and that patient and disease characteristics like age, PN volume or number of PN-related morbidities are expected to be treatment effect modifiers. All these associations are not captured by the current model.

The ERG acknowledges the limitations of the available data from SPRINT and that robust statistical analyses are challenging. However, it should be emphasised that the same data were used to inform the company's AUC model. Therefore, the ERG is not convinced that this modelling approach provides a reliable estimate of the cost-effectiveness of selumetinib: data limitations and uncertainties are present in the AUC model. Also, while it can be argued that AUC models minimise the number of assumptions required compared with more complex models, this does not imply that the assumptions made for the AUC model are automatically valid. The AUC choice may seem pragmatic, but the committee should be aware that it also has limitations and might rely on strong assumptions and was simplistically implemented. The ERG would argue that a patient-level model, using the same data, but in terms of PN growth rate, might be more useful for decision-making.

Similar limitations also apply to HRQoL data. Given the lack of patient-level HRQoL data from the Natural History study, no treatment effect could be determined for selumetinib. Also, given the limited availability of PedsQL data, no robust association could have been identified between for example PN volume or PN growth rate and HRQoL.

Furthermore, the evidence provided in the CS supports the assumption that PFS should also be a health state in the comparator arm of the model. This potential issue was raised by the ERG in the clarification letter, however, the company still considered appropriate to assume that patients in the BSC arm stay in the progressive disease health state for the whole duration of the analysis while evidence shows that in the BSC arm there are patients in PFS who do not seem to progress (or to progress slowly).[53] Furthermore, it is unclear why the company have not tried to use for this purpose the results of the propensity score analyses presented in Section 4.2.4.3 of this report. These results were reported as HRs for PFS which in principle could be directly implemented in the economic model, despite the limitation highlighted in aforementioned Section.

There is substantial uncertainty in selumetinib PFS over the long-term due to the immaturity of PFS data and limited follow-up of 3 years. It is unclear how reflective the annual progression probability of 5.6%, which is equivalent to a simple exponential distribution, is over the long-term. Kaplan-Meier curves and fit statistics were not presented, so the fit of this exponential curve to the data available could not be assessed. The ERG believes that, despite the limitations, the company should have attempted to conduct full survival analyses as done with time to treatment discontinuation data.

The assumption that no progression events occur after the age of 18 years is potentially problematic for two reasons:

- Firstly, no evidence was presented that progression would never occur over the age of 18 years. Data from the Natural History study presented in Table 13 of the response to request for clarification (in response to question B3) showed that PFS continued to decline (albeit not steeply) to year 5 in patients who started the study aged 16+ (PFS year 1= [redacted]; year 2= [redacted]; year 3= [redacted]; year 4= [redacted]; year 5 = [redacted]), suggesting some progression events will occur after the age of 18, although fewer events than in the younger age groups.[53] If some progressions would occur in clinical practice, even if only a few, this assumption would favour selumetinib as these patients are artificially held at a higher utility in the model, while all BSC patients are assumed to be progressive.
- Secondly, if it is to be accepted that tumour growth does plateau to the extent that no progressions occur after 18 years, then the inclusion of older adolescent patients in the SPRINT trial may have biased results if they would not be expected to progress regardless of treatment, which artificially increases the proportion of patients who remain progression free in the trial and model results. The company presented data on change in PN volume from the Natural History study, separated by age group in their clarification response.[53] These data show a trend for smaller percentage changes in tumour volume over the age of 12 years, with substantially lower likelihood of progression from the age of 16 years. Therefore, it would appear that patients aged 16 years and above in the SPRINT trial would be unlikely to progress, regardless of treatment. Figure 6 of the response to the request for clarification shows that [redacted] SPRINT participants were over the age of 15.5 years.[53]

The ERG also noted that in Tables 23 and 29 of the CS, which summarise the baseline characteristics of the SPRINT participants in Phase I and Phase II Stratum II, respectively, that 9 (38%) and 11 (44%) of patients, respectively, were classed as having progressive PN growth at baseline (defined as ≥20% increase in PN volume within 15 months prior to enrolment).[1] It is unclear whether these patients would

have a lower, higher or equivalent chance of experiencing progression during SPRINT compared to those classed as stable at baseline.

For the modelling of TTD, the company performed a series of parametric extrapolations of patient-level data from SPRINT Phase II Stratum I. From these, the Weibull curve was selected as the most appropriate extrapolation. The ERG considered the approach to extrapolation as well as the selection of the curve for the base-case model as appropriate and did not make any changes for the ERG preferred base-case.

The modelling of mortality (through an SMR applied to general population mortality estimates) was appropriate for the model structure selected by the company. The assumption of equal mortality rates in both treatment arms may be considered as a conservative approach. The SMR used by the company in the model was sourced from Duong et al. 2011 and pertained to an estimate across all age groups.[78] However, that study shows that the only significant differences in mortality occurred in age groups 10 to 20 years and 20 to 40 years. The current cohort model approach does not allow to model excess mortality differently for specific age groups, which would only be possible if these two were linked, e.g. using a patient-level model.

Grade ≥3 AEs that occurred in greater than 5% of patients in SPRINT were included in the model. No disutilities were included in the model for these adverse events. The ERG requested that these be included at clarification, but the company declined.[53] Given the short duration for all but dermatitis acneiform and the low incidences, it is unlikely that this has a large impact on results, however for completeness these should have been included.

HRQoL was measured using the PedsQL in the SPRINT trial, which is a non-preference based generic instrument for measuring QoL in children. The company chose not to map these data and to conduct a vignette TTO study to estimate utility values for on-treatment and progressive disease health states for the model. Vignette TTO studies are associated with a range of limitations, the most important of which being that they do not meet the HRQoL measurement aspect of the NICE reference case, which requires that HRQoL is measured directly in patients or carers. In the vignette study, health state descriptions were created and provided to members of the general population for direct valuation. It is unclear how accurately members of the general population are able to imagine a health state from only a description, particularly in a case such as this where the condition is rare, widely unknown, and not easy to conceptualise, with health states centred on a "large lump" and its impact on various aspects of HRQoL.

Additionally, health state descriptions were lengthy which could lead to the use of heuristic shortcuts and use of bolding may have focussed participants on the more positive elements of the treated state and the more negative elements of the untreated state encouraging focussing effects and a larger implied treatment effect than may have occurred without bolding. However, in the absence of alternative data and after the company's refusal to map the available PedsQL data in SPRINT to EQ-5D utilities, the ERG had no alternative health state utility values available for their base-case and no change could be made.

Carer disutilities were estimated by applying the same relative HRQoL decrement as that applied to patients (patient treatment effect = [redacted]). This disutility was applied to 1.4 carers per patient, as the average household size in the UK is 2.4 persons. No evidence specific to carers in this population was presented to substantiate either of these assumptions. A recent review of carer disutilities in NICE appraisals showed that the assumed disutility of approximately [redacted] was substantially larger than disutilities applied in other appraisals, including a disutility of 0.11 for caring for a non-ambulatory

child with DMD and a disutility of 0.07 for carers of children with activity limitations. The ERG did not consider the assumption that everyone except the patients in an average household UK would be a carer appropriate, as there could well be other children in the household. Given that most appraisals which included a carer disutility had applied it to only one carer, this approach was considered more appropriate given the lack of data. The ERG considered a disutility of 0.07 for carers of children with activity limitation applied to one carer more appropriate for their base-case.

In the model, the company assumed that all patients entered in a progressive state with a utility of [redacted]. Patients receiving selumetinib were assumed to experience a linear increase over 1 year to the on-treatment utility value of [redacted], which was applied until progression. The company assumed that upon progression, patient's utility linearly declines from [redacted] to [redacted] over a period of 5 years. No justification was provided as to why 5 years was assumed. This assumption is combined with another which assumes that patients' utility remains the same from the age of 18 as no progression events are assumed to occur beyond this age as tumour size is assumed to plateau. If a patient experiences a progression event prior to 18 but has not yet reached the progression state utility of [redacted], they keep that mid-way utility for the remainder of their lifetime. Therefore, the treatment benefit observed at 18 is considered a lifetime benefit of treatment. Stability of utility after 18 years of age, combined with a 5-year post-progression waning can provide a substantial lifetime treatment benefit for which no evidence is presented. The ERG considers a linear decline in utility over one-year post-progression to be more appropriate, given that a) this equals the period assumed to observe the full treatment effect at treatment initiation and b) that the vignettes upon which progression free and progressive utility values are based are not based on a certain lump (PN) size, but only on the fact that the lump is growing, and no treatment is being received. This applies from progression.

The ERG also considers it inappropriate that treatment discontinuation has no impact on utility in the model. Only progression is assumed to impact utility. Therefore, changing the discontinuation rate or extrapolation model has no impact on QALYs. This is unrealistic, given that it is assumed that all patients not receiving treatment in the BSC arm will have progressive disease, which is associated with a much lower utility, but the same assumption is not applied in the selumetinib arm, which will bias results in favour of selumetinib.

Regarding health care resource use and costs, the analysis included drug acquisition costs for selumetinib, the costs of additional MRI scans for patients receiving selumetinib, pain medication costs, and costs for the medication used in the management of treatment-related AEs. This was considered, both by the company and the ERG, to be only a limited set of cost items, since not all cost items that are potentially relevant were included. The company indicated that this was due to the heterogeneity in patient and symptomatic management and that there is no specific data to support a quantitative difference in the symptom management costs other than pain medication costs. The ERG considers it plausible that any relevant disease management costs (i.e. other than costs in relation to the additional monitoring requirements or management of treatment-related AEs that are specific for treatment with selumetinib) will be reduced following treatment with selumetinib. Therefore, the ERG agrees with the company that the simplification to exclude these costs may be seen as a reason to interpret the cost effectiveness results as conservative estimates.

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

In this chapter the changes made by the ERG to the cost effectiveness model provided by the company are outlined. These changes were divided into the following three categories (as defined by Kaltenthaler et al. 2016):[92]

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope, or best practice has not been adhered to)
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred)

These changes were implemented in the company's model to define the ERG base-case. Additionally, scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

6.2 Explanation of the ERG adjustments

No errors or violations that could be corrected by the ERG were identified in the economic model, except for the PSA adjustments discussed in Section 5.4.2.2. Additionally, the following issues were discussed in Section 5 and can be regarded as matters of judgement:

1. The ERG prefers using a caregiver disutility equal to 0.07 instead of assuming that the impact of caring was equivalent to the impact of moving from stable to progressive disease for patients ([redacted]), see Section 5.3.3.7 for details.
2. The ERG prefers assuming that the carer disutility will be applied to one caregiver instead of 1.4 given that there is no evidence that more than one caregiver is required in this population, and this is commonly assumed in previous NICE appraisals which have included caregiver disutilities, see Section 5.3.3.7 for details.
3. The ERG prefers assuming a waning of utility after progression over 1 year instead of 5 years as utility was assumed to only take 1 year to increase to the on-treatment utility upon treatment initiation and no evidence was provided as to why the reverse process upon progression should take 5 years. Additionally, the vignette used to estimate a utility value for the progressive state describes a situation where the lump (PN) is growing, and no treatment is received. This already applies at the time of progression, see Section 5.3.3.7 for details.
4. The ERG prefers assuming four MRIs per year for selumetinib instead of two, in line with clinical expert opinion that was obtained by the company.

6.3 ERG base-case results

The results from the ERG deterministic base-case are shown in Table 6.1. Overall, selumetinib costs an additional [redacted] for a QALY gain of [redacted], resulting in an ICER of £134,410 per QALY gained compared to BSC.

Table 6.1: ERG base-case results, discounted

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	134,410
Based on electronic model with ERG preferred assumptions BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year							

Table 6.2 shows the individual changes implemented from the company base-case to the ERG base-case and their cumulative impact on the ICER (each step is added to the previous changes already implemented). The ERG base-case results were taken from Table 6.1 and the company base-case results from Table 5.13. The changes which had the largest impact on the ICER were using a caregiver disutility equal to -0.07 and assuming a waning of utility after progression over 1 year.

Table 6.2: Cumulative impact of the ERGs preferred model assumptions

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company base-case	5.4.1	[redacted]	[redacted]	93,169
ERG change 1 – caregiver disutility equal to -0.07	5.3.3.7	[redacted]	[redacted]	117,352
ERG change 2 – carer disutility applied to 1 caregiver	5.3.3.7	[redacted]	[redacted]	121.278
ERG change 3 – waning of utility after progression over 1 year	5.3.3.7	[redacted]	[redacted]	133,912
ERG change 4 – four MRIs per year for selumetinib	5.3.3.8	[redacted]	[redacted]	134,410
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Ínc. = incremental; MRI = magnetic resonance imaging; QALY = quality adjusted life year				

The ERG also conducted a PSA on their preferred base-case, with results shown in Table 6.3. The probabilistic ICER, averaged over 10,000 simulations, was £127,067, which is in line with the deterministic ICER shown in Table 6.1.

Table 6.3: ERG probabilistic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	127,067
Based on electronic model with ERG preferred assumptions BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year							

Figure 6.1 shows the scatterplot of the PSA outcomes on the CE-plane. [redacted]. Based on

these, the CEAC was derived and shown in Figure 6.2. At the threshold ICER of £100,000 per QALY gained, the probability that selumetinib is cost effective compared to BSC is [redacted]%.

Figure 6.1: PSA scatterplot ERG base-case

Based on electronic model with ERG preferred assumptions
ERG = Evidence Review Group; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 6.2: Acceptability curve ERG base-case

Based on electronic model with ERG preferred assumptions
BSC = best supportive care; ERG = Evidence Review Group

6.4 Exploratory scenario analyses conducted by the ERG

The ERG conducted several additional scenario analyses to explore model uncertainties. The results of these scenarios are summarised in Table 6.4 and described below. Age was not varied in scenario analyses because, as explained in Section 5.4.2.3, the ERG considers that these scenarios can be misleading. Also, the ERG did not conduct any scenarios varying assumptions on mortality and resource use/costs due to minimal impact on the results shown by the company analyses also in Section 5.4.2.3.

6.4.1 Scenario set 1: Progression-free survival

This analysis considered a CI of [redacted]% to [redacted]% for the cumulative probability of progression by year 3 (base-case was [redacted]%), as in Section 5.4.2.3. At the lower bound the ICER decreased to £104,507 per QALY gained and increased to £176,911 per QALY gained at the upper bound. These scenarios only led to changes in QALYs because in the model there are no costs associated to being in the PFS health state.

6.4.2 Scenario set 2: Alternative parametric distributions for TTD and maximum treatment duration

All available parametric distributions for TTD extrapolation were explored by the ERG. As in the company base-case, the Weibull distribution was the preferred option for the ERG. All scenarios resulted in ICERs higher than in the base-case analysis. This is because, as explained above, in the model TTD only impacts total costs but not QALYs since TTD is not linked to PFS or HRQoL. Therefore, the results from these scenario analyses should be interpreted with caution.

The ERG also explored the impact of changing the maximum treatment duration on the model results. In the base-case this was 8 years. The ERG considered scenarios where treatment duration was limited to 1 year, 3 years, 5 years, and 10 years, and one scenario where no maximum duration was assumed. In this case, the ICER increased with the treatment duration assumed. However, it should be again emphasised that in these scenarios changing TTD assumptions only changed total costs. Thus, the results from these scenarios should also be interpreted with caution.

6.4.3 Scenario set 3: Health-related quality of life

Patient utility: Given that no alternative sources of utility values for inoperable NF1 PN were identified, and the company declined to map the PedsQL data from SPRINT, the ERG conducted scenarios using the upper and lower bounds of the CI for the included utility values from the vignette study. The ICERs ranged from £88,799 to £159,603 per QALY gained.

Parent/carer utility (relative difference): The company assumed that the impact of caring was equivalent to the relative impact of the disease of patients (patient treatment effect [redacted]). This decrement was applied to 1.4 carers. The ERG preferred to assume a carer disutility of 0.07 applied to one carer. Scenarios representing the company and ERG preferred disutilities in 1.4 and one carers were conducted to examine the impact of these assumptions on results. Company scenarios assuming that carer disutilities were applied over the caregivers' lifetime (rather than up until the patient reached 18 years of age) and assuming that the disutility due to caring was 75% and 50% of the burden of the disease on patients were also conducted.

Alternative assumptions on utility change over time: The time period over which HRQoL was assumed to reach the on-treatment value of [redacted] upon treatment initiation was varied between the base-case value of 1 year and 5 years. The time period over which HRQoL was assumed to wane to the progressive utility value of [redacted] upon progression was varied between the ERG's preferred 1 year and

the company's preferred 5 years. A scenario where the age-adjustment of utility was removed was also conducted. In these scenarios, the ICERs varied from £121.729 to £140,328 per QALY gained.

6.4.4 Scenario set 4: Other scenarios

Alternative discount rates: The impact of discounting results by 1.5% decreased the ICER from £134,410 by more than £95,567 per QALY gained.

BSA approach: The company considered different approaches to implementing BSA in their economic model. As explained in response to clarification question B19.a, the option *"BSA from SPRINT"* allows the user to enter a baseline BSA, which then increases on an annual basis by adding the age coefficient defined on the *"BSA_PopUp"* tab of the model.[53] Alternatively, the option *"BSA calculated using linear regression"* uses the linear regression in Table 5.9 to estimate BSA at baseline using patients' age also at baseline. BSA then increases following the regression line. This results in differences in BSA estimates, which results in differences in the ICER. In particular, the option *"BSA calculated using linear regression"* increased the ICER from £134,410 (ERG base-case based on *"BSA from SPRINT"*) to £146,546 per QALY gained.

Table 6.4: ERG scenario analyses results

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£)
ERG base-case	Section 6.3 of this report	[redacted]	[redacted]	134,410
PFS – cumulative probability of progression by year 3	[redacted]%	[redacted]	[redacted]	104,507
	[redacted]%	[redacted]	[redacted]	176,911
Alternative parametric distributions for TTD	Exponential	[redacted]	[redacted]	144,148
	Generalised gamma	[redacted]	[redacted]	147,749
	Gompertz	[redacted]	[redacted]	136,930
	Loglogistic	[redacted]	[redacted]	144,701
	Lognormal	[redacted]	[redacted]	151,750
Maximum treatment duration (base-case 8 years)	1 year	[redacted]	[redacted]	16,649
	3 years	[redacted]	[redacted]	65,980
	5 years	[redacted]	[redacted]	101,548
	10 years	[redacted]	[redacted]	145,894
	No maximum duration	[redacted]	[redacted]	160,312
Patient utility	Upper CI bound for untreated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	88,799
	Lower CI bound for treated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	159,603
	Lower CI bound for untreated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	121,467
	Upper CI bound for treated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	116,085
Parent/carer utility	Relative difference 75%	[redacted]	[redacted]	111,207
	Relative difference 50%	[redacted]	[redacted]	121,274
	Impact for duration parent/carer lifetime	[redacted]	[redacted]	110,945

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£)
	Disutility of 0.07 for 1.4 carers	[redacted]	[redacted]	129,621
	Relative impact on carers equal to relative impact on patients (patients = [redacted]) for 1.4 carers (company BC)	[redacted]	[redacted]	102,683
	Relative impact on carers equal to relative impact on patients (patients = [redacted]) for 1 carer	[redacted]	[redacted]	112,541
Utility change over time	Years to achieve treated HRQoL after initiating treatment: 2 years	[redacted]	[redacted]	137,102
	Years to achieve treated HRQoL after initiating treatment:3 years	[redacted]	[redacted]	140,328
	Years to revert to baseline HRQoL after progression (2 years)	[redacted]	[redacted]	131,006
	Years to revert to baseline HRQoL after progression (3 years)	[redacted]	[redacted]	127,768
	Years to revert to baseline HRQoL after progression (5 years)	[redacted]	[redacted]	121,729
	Age-adjusted utility not included	[redacted]	[redacted]	123,885
Alternative discount rates	1.5% for costs and outcomes	[redacted]	[redacted]	95,567
BSA approach	Calculated using linear regression	[redacted]	[redacted]	146,546

Based on electronic model with ERG preferred assumptions

BSA = body surface area; BSC = best supportive care; CI = confidence interval; ERG = Evidence Review Group; HRQoL = health related quality of life; ICER = incremental cost effectiveness ratio; Incr. = incremental; PFS = progression-free survival; QALY = quality-adjusted life year; TE = treatment effect; TTD = time to discontinuation

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

The CS includes a budget impact analysis to estimate the total costs to the NHS and PSS, for a period of 5 years of adopting selumetinib in England. As explained in Section 2.2.2, the anticipated license for selumetinib is paediatric patients aged 3 to 17 years.

- Based on ONS estimates, 10,140,338 children are in this age range in England and Wales (mid-2020).[13, 14]
- The total number of admissions of neurofibroma in England was 538, based on hospital episode statistics for primary diagnosis of NF (assumed mostly NF1).
- The company identified research suggesting that approximately 25% of NF1 paediatric patients will have a PN,[18, 19] and that approximately 55% of PN are symptomatic.[20]
- An inoperable PN is defined as "*being unable to be completely surgically resected without risk of substantial morbidity due to encasement of, or proximity to, vital structures, invasiveness, or level of vascularisation*".[1] A range between 43% and 57% of PN is estimated to fulfil this definition of inoperability.[13, 14] For their budget impact analysis, the company assumed the midpoint of this range (50%).
- This led to an estimated 37 prevalent paediatric NF1 patients with symptomatic PN eligible for selumetinib in England within the licensed population. Calculation details are presented in Table 2.1 of this report.

The estimated uptake and compliance rates of selumetinib over the next 5 years are based on internal estimates from the company. Furthermore, the budget impact analysis incorporated an annual average treatment discontinuation based on the SPRINT Phase II Stratum I TTD data. The estimated budget impact of selumetinib over the next 5 years is shown in Table 7.1. This resulted in a net budget impact of [redacted] in year 1 and [redacted] in year 5 (net cumulative budget impact over years 1 to 5 was [redacted]).

Table 7.1: Company budget impact analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients (paediatric symptomatic, inoperable NF1 PN)	37	37	37	37	37
Selumetinib uptake/compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population on treatment with selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive current clinical management (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of treatment pathway without selumetinib*	£0	£0	£0	£0	£0
Cost of treatment pathway with selumetinib (net budget impact)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Tables D37 and D38 in the CS[1]
Note: Totals may not appear to be the sum of the parts due to rounding.
* The company assumed that there are no costs associated with BSC, since these are minimal. Because selumetinib will be administered in addition to BSC, any incremental impact is assumed to be negligible.
BSC = best supportive care; CS = company submission; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibromas

7.2 ERG critique of the company's budget impact analysis

Several assumptions made by the company in the budget impact analysis could not be validated by the ERG.

There is no reference provided for the total number of admissions of neurofibroma in England. This was estimated as 538 by the company, but it is only mentioned that was based on hospital episode statistics for primary diagnosis of NF.

Also, the estimated uptake and compliance rates of selumetinib over the next 5 years were based on internal estimates from the company. However, no explanation was given regarding how these estimates were calculated or whether they have been validated by experts or not.

Furthermore, the company mentioned that the budget impact analysis incorporated an annual average treatment discontinuation based on the SPRINT Phase II Stratum I TTD data, but it is unclear what exact values were used to derive the estimates in Table 7.1, as the ERG could not trace these values in the economic model. This results in a total number of patients treated with selumetinib not increasing after year 3, which might seem counterintuitive. Likewise, it is also unclear what total annual costs were applied in Table 7.1 since these could not be found in the economic model.

Finally, as explained in Section 2.2.2 of this report, when using data from Nguyen et al. 2011 regarding the proportion of paediatric NF1 patients with PN (57%), and the revised data regarding the proportion of those patients who are symptomatic (46%), the estimated number of eligible patients increased from 37 to 70.[18] To account for the potential increase in of patients with NF1 and PN being eligible/considered for selumetinib treatment, the ERG repeated the calculations from the company, but now starting from 70 eligible patients.

The estimated budget impact of selumetinib over the next 5 years estimated by the ERG is shown in Table 7.2. This resulted in a net budget impact of [redacted] in year 1 and [redacted] in year 5 (net cumulative budget impact over years 1 to 5 was [redacted]). Note, however, that the same uncertainties discussed above, also apply to the ERG estimates.

Table 7.2: ERG budget impact analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients (paediatric symptomatic, inoperable NF1 PN)	70	70	70	70	70
Selumetinib uptake/compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population on treatment with selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive current clinical management (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without selumetinib*	£0	£0	£0	£0	£0
Cost of treatment pathway with selumetinib (net budget impact)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Table 7.1
Note: Totals may not appear to be the sum of the parts due to rounding.
* The company assumed that there are no costs associated with BSC, since these are minimal. Because selumetinib will be administered in addition to BSC, any incremental impact is assumed to be negligible.
BSC = best supportive care; ERG = Evidence Review Group; NF1 = type 1 neurofibromatosis; PN = plexiform neurofibromas

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Proportion of costs or benefits which fall outside of the NHS and PSS

The company have not estimated the proportion of costs outside of the NHS and PSS that may be saved due to treatment with selumetinib, or of the additional benefits other than health. Only in Sections 8.1.2 to 8.1.4 of the CS some narrative is presented to detail potential savings outside of the NHS and PSS.

8.1.2 Societal costs

The CS states that while the impact of selumetinib on cost and cost savings to UK government bodies has not been explicitly investigated, selumetinib may be expected to bring cost savings to government bodies other than the NHS as a result of improvements in patients' daily lives (e.g., improved school attendance), reduced patient disability, and improved parent/carer productivity.[1]

8.1.3 Costs borne by patients

In the CS it is indicated that parents and other carers often experience a loss of income due to time spent on caring for the patient.[1] Costs may occur when home adaptations and aids are required. Additionally, for adult patients some costs may also occur for vision aids. However, none of these costs were quantified in the CS.

8.1.4 Other carer costs

In the CS the findings of interviews with UK clinicians are discussed.[30] The interviewees indicate that family, often the parents, of the patient spent a substantial amount of time on care, leading to loss of productivity. This may continue into adulthood of patients. This time on care was not quantified.

8.1.5 Impact of the technology on research and innovation

According to the CS, selumetinib represents a step change in the management of NF1 PN as it is the first licensed disease-modifying treatment for NF1 PN.[1] This may lead to increased understanding of the long-term impact of disease-modifying treatment for PN, which might lead to further innovations in the care of patients with symptomatic, inoperable PN.

ERG comment: The CS only includes some narrative about costs outside the NHS and PSS, without any quantification. The company reason that some of these costs may be saved when patients are treated with selumetinib, given that the treatment may reduce PN-associated morbidities. However, there is currently no evidence to indicate to what extent reduced morbidity will also lead to savings in societal, patient, and carer costs.

8.2 Staffing and infrastructure requirements associated with the use of the technology

Selumetinib will be delivered from the two UK NF1 PN specialist centres by clinicians experienced in the treatment and management of patients with NF1 PN. As a safe, oral treatment, it is anticipated that no major changes to the way current services are delivered (both with regards to staffing and infrastructure) would be required for the introduction of selumetinib.

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

As reported in Section 4.1.1, the company searched a broad range of resources, including supplementary searches of conference proceedings and other relevant resources such a trials database, company records and the checking of references lists to identify additional studies not retrieved by the main searches. Individual strategies were well constructed and contained a combination of subject heading index and free text terms. Searches were clearly reported and reproducible. A few minor errors were identified, however, these are unlikely to have impacted on the findings of the literature reviews.

As detailed in Section 4.2.1, the ERG considered two additional studies to be relevant to the NICE final scope.[55, 56] These provided further results regarding AEs.

Clinical efficacy results were presented from the SPRINT Phase II Stratum I trial (recruiting 50 patients from four centres in the USA), and comparisons were made with the NCI Natural History study (93 age-matched individuals) and the placebo arm of the tipifarnib study (29 participants). These are reported in Section 4.2.4 and summarised below:

- Results suggested that more participants receiving selumetinib in SPRINT Phase II Stratum I experienced a reduction in PN volume of at least 20% when compared with usual care in the NCI National History study (68% vs. 0%).
- 45 patients (90%) treated with selumetinib in SPRINT Phase II Stratum I had BOR of reduction in PN volume from baseline, and 37 patients (74%) experienced at least 20% reduction in PN volume at BOR.
- The median time to initial response in SPRINT Phase II Stratum I was 8 cycles (range 4 to 20), and the median time to best response was 16 cycles (range 4 to 36).
- None of the participants receiving selumetinib in SPRINT Phase II Stratum I displayed a PN growth rate of 20% or more per year (range -27.0% to 19.8% per year), compared with 43% of patients in the age-matched cohort of the NCI Natural History study.
- The median PFS was not reached in SPRINT Phase II Stratum I at DCO 29 March 2019. At 3 years, 84% of patients in SPRINT Phase II Stratum I remained progression-free compared with 15% in the NCI Natural History age-matched cohort.

With respect to safety and AEs, at a DCO of 29 March 2019 for the SPRINT Phase II Stratum I study, [redacted] of patients experienced AEs, [redacted] of patients experienced Grade ≥3 AEs, and [redacted]. Results for two additional studies, reporting on 28 participants, are in line with these findings, details can be found in Section 4.2.4.2.

As there were no head-to-head trials comparing selumetinib to established clinical management, naïve comparisons were conducted between SPRINT Phase II Stratum I, an age-matched cohort from the NCI National History study, and the placebo arm of the tipifarnib study. In addition, to explore the potential impacts of adjusting for baseline covariates across the study population, the company undertook a propensity score analysis. The results showed a statistically significant advantage of selumetinib compared to 65 participants of the Natural History age-matched cohort, e.g. [redacted]. Results were highly consistent across all four additional analyses and demonstrated a high degree of robustness to the choice of method used for comparison. However, these results were based only on PFS, where progression was defined as ≥20% increase in PN volume, which was not listed in the NICE final scope.

9.2 Statement of principal findings – cost effectiveness

The company conducted a CEA to assess the cost effectiveness of selumetinib in NF1 PN. The company base-case results estimated [redacted] incremental QALYs accrued by selumetinib compared to BSC at an additional cost of [redacted]. This corresponds to an ICER of £93,169 per QALY gained.

The ERG amended some of the assumptions made by the company in their base-case. In the results from the ERG deterministic base-case, selumetinib costs an additional [redacted] for a QALY gain of [redacted], resulting in an ICER of £134,410 per QALY gained compared to BSC. The changes which had the largest impact on the ICER were using a caregiver disutility equal to -0.07 and assuming a waning of utility after progression over 1 year. The ERG PSA yielded an ICER of £127,067, which is in line with the deterministic ICER. When plotted on the CE-plane, [redacted]. Based on these, the CEAC was derived and at the threshold ICER of £100,000 per QALY gained, the probability that selumetinib is cost effective compared to BSC was [redacted]%. The ERG scenarios which had the largest impact on results were assuming alternative rates of progression, the length of the maximum duration of selumetinib treatment, assigning utilities to patients and to parents/caregivers and using 1.5% discount rates on costs and health effects.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG believes that the following represent strengths within the CS:

- The DP addressed in the CS aligns with the NICE final scope.
- Searches for clinical effectiveness evidence were well conducted.
- The CEA was performed in line with the NICE final scope. Thus, it is relevant for the DP addressed in this submission.
- The company presented the first CEA for children with NF1 PN. The analysis aligns with the NICE reference case. The model developed reflects to some extent the disease progression and its impact on HRQoL.
- Time on treatment is based on parametric extrapolations of patient-level data from SPRINT Phase II Stratum I that were performed appropriately.
- The company also attempted to address the evidence gaps around utilities by conducting a novel TTO study specifically aimed at eliciting NF1 PN utility values.

9.3.2 Weaknesses of the CS

The following are the main weaknesses of the CS, observed by the ERG:

- The clinical effectiveness evidence comes from small single-arm studies.
- The SLR conducted for the clinical effectiveness section does not follow best practice.
- Two additional studies, identified by the company, are relevant to the DP.
- The economic model does not capture the heterogeneity and important aspects of the natural progression of the disease: in particular, PFS precludes the effect of variation in PN growth rate.
- The modelling approach to PFS is simplistic, applying a constant annual probability of progression and only for selumetinib.
- The results of the propensity score analyses conducted for the assessment of the clinical effectiveness were not implemented in the economic model.
- The assumption of 5-year waning of utility after progression is unclear.

- No relationship between time on treatment and clinical effectiveness or HRQoL was modelled.
- No reduced mortality rate with selumetinib was modelled, despite the disease modifying nature of treatment with selumetinib and possible impact on mortality.
- The HSUVs and the caregiver disutilities used in the model are highly uncertain.
- The analysis includes only a limited number of cost items, and costs that are potentially relevant in relation to patient and symptomatic management were excluded.

9.4 Uncertainties

The size of the total population eligible for selumetinib might be bigger than indicated in the CS. This has been explored in a budget impact analysis, see Sections 2.2.2 and 7.2.

As discussed in Section 4.2.1, participants of SPRINT Phase II Stratum I were recruited in the USA which might limit the generalisability to patients in the UK.

The ERG considers that the cost effectiveness results are subjected to substantial structural uncertainty since it is unclear whether the structure of the economic model is appropriate to model the natural progression of the disease. NF1 and PN are heterogenous and the evidence provided by the company suggests that disease progression, including PN growth rate, varies with age. Besides age, disease characteristics like PN volume or number of PN-related morbidities are expected to be treatment effect modifiers. All these associations are not captured by the current model, and while a patient-level model might capture some of them, it is unknown what the impact on the cost effectiveness estimates would be. A second source of structural uncertainty relates to the modelling of PFS. This seems inappropriate in general. For the selumetinib arm applying a constant annual probability of progression seems too simplistic, is not well justified and there is no possibility to change this in the model. Also, despite the evidence presented by the company suggesting otherwise, there is no PFS modelled in the BSC arm: patients are assumed to remain in the progressed disease health state. A full parametric modelling in the selumetinib arm and including PFS in the BSC arm (followed also by a full parametric modelling) should resolve some of the structural uncertainty, which in turn will be "replaced" by parameter uncertainty. Given the lack of data, this "new" parameter uncertainty is expected to be large, however, it should be assessed by a standard PSA. It is unknown what the impact of an alternative modelling of PFS on the cost effectiveness estimates would be but including PFS in the BSC arm is expected to increase the ICER.

Despite the disease modifying nature of treatment with selumetinib and possible impact on mortality, no reduced mortality rate with selumetinib is modelled. If there were evidence available that could be used to model a possible reduction in mortality with selumetinib, this is expected to decrease the ICER.

The ERG considers that the utility values included in the model are associated with a substantial amount of uncertainty as they are not based on measurements of HRQoL directly from patients/carers, it is unclear how well members of the general population were able to conceptualise this rare disease based on vignettes and it is unclear how the length of the descriptions and use of bolding would have affected the use of heuristic shortcuts and focussing effects on respondents. HRQoL data from patients/carers is required to better understand the impact of the condition on HRQoL and quantify the treatment effect in terms of utility. Data from carers in this population is also required to understand the disutility associated with caring.

Another major uncertainty in the HRQoL submission is how progression and discontinuation impact utility. The assumption of a linear decline in utility over 5 years after progression is unsupported by evidence and unreflective of the health state vignette used to describe a progressive state. The model

also assumed that discontinuation had no direct impact on utility, which does not seem realistic given that all patients receiving BSC are assumed to experience progressive disease.

An important source of uncertainty relates to the inclusion of only a limited number of cost items, and exclusion of potentially relevant cost items in relation to patient and symptomatic management. As such, the analysis does not provide a comprehensive overview of relevant costs. There is no data available to inform health care resource use for patients treated with selumetinib, but it is likely that patient and symptomatic management costs will be reduced in these patients. Therefore, the exclusion of these costs may be a reason to interpret the cost effectiveness results as conservative estimates.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Tuesday 26 October 2021** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 N/A

Issue 2 Reporting of NF1 PN population size calculations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 27: The ERG report states that "values were derived from taking the total number of admissions of neurofibromatosis in patients aged 3 to 17 years (n=538) and subtracting the proportion of these patients who 1) do not have PN (calculated at 75%), 2) who have asymptomatic PN (calculated at 45%), and 3) have symptomatic but *inoperable* PN (calculated at 50%)."	The final point should read "[…] have symptomatic but *operable* PN (calculated at 50%)."	The proposed amendment provides a more accurate representation of how the population eligible for selumetinib was calculated, as the number of patients with symptomatic but *operable* PN was subtracted from the population to give the number of patients with symptomatic but *inoperable* PN.	Changed accordingly.

Issue 3 Assessment of the SLR methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Throughout multiple sections of the report, the ERG states that the SLR conducted by the company did "not follow best practice" (e.g. page 87) or that methods "were not in line with best practice" (e.g. page 15).	We would propose changing corresponding wording throughout the report to state that the SLR did "not *fully* follow best practice" or that methods were "not *entirely* in line with best practice", for example.	While we acknowledge that the SLR approach slightly deviates from published best practice for the points mentioned in the report, we consider it more accurate to also reflect that the methods are otherwise, and for the most part, aligned with available best practice.	Not a factual inaccuracy.
Page 43: The ERG report states	We would suggest including additional wording	The proposed amended reflects	Not a factual inaccuracy.

that "the company *conducted quality assessments on two studies not identified in the clinical SLR and on the SPRINT Phase II Stratum I study,* considered by the company to be of greatest relevance to the DP." It further states that "in questions A8 and A15 of the clarification letter, the ERG probed into why seven of the eight relevant clinical SLR studies were not included in the main body of the CS *(which would warrant a quality assessment)*."	to state that "*additional quality assessments for the remaining studies were provided together with further details on the respective studies in the appendix*." We would further request for the wording "*which would warrant a quality assessment*" to be removed from this sentence.	more accurately that critical appraisals were indeed provided for the studies not included in the main body of the submission (together with the respective extractions of these studies in Appendix 2 of the submission).	
Page 43: The ERG report states that "in the response to the request for clarification*, the company provided no justification for this, but rather reiterated the relevance of these identified studies in the CS*."	We would suggest changing the wording, to say that "in the response to the request for clarification, *the company provided their assessment of relevance to the DP for each of the eight studies (Table 4.4)*."	The proposed amendment more accurately reflects that the relevance of all eight identified studies was discussed in order to explain the inclusion of only SPRINT Phase II Stratum I as part of the main body of the submission.	Not a factual inaccuracy.
Page 46: The ERG report states that "in the reply to question A8, the company stated that all studies listed in Table C3 of the CS *were relevant for inclusion*. However, as part of the reply to question A15, the company tabulated reasons for *excluding the seven studies in question*."	We would propose changing the wording, to say that "in the reply to question A8, the company stated that all studies listed in Table C3 of the CS *met the pre-defined inclusion criteria*. However, as part of the reply to question A15, the company tabulated reasons for *not including the seven studies as part of the main body of the submission.*"	The proposed amendment more accurately reflects the selection of identified studies for the main body of the submission.	Not a factual inaccuracy.
Page 87: The ERG report states that "*Two additional studies,*	We would suggest including additional wording, to say that "Two additional studies, identified by	The proposed amendment provides further relevant context for the two	Not a factual inaccuracy.

identified by the company, are relevant to the DP."	the company *and reporting AE data in line with the findings from SPRINT Phase II Stratum I*, are relevant to the DP."	additional studies.	

Issue 4 Reporting of the propensity score analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 16: With regards to helpful additional evidence for key issue 3, the ERG listed "*further propensity score matching based on the outcomes listed in the NICE final scope, particularly growth rate of PN, and implementation of the results in the economic model.*"	The report should be amended throughout to reflect that additional propensity score analyses *based on annual growth rates of target PN (absolute or relative change in target PN volume) and Objective Response Rate* have been provided as part of the clarification questions (A10 a) and b)).	The proposed amendment more accurately reflects the evidence provided over the course of the submission process.	Changed accordingly.
Page 16: For the description of key issue 3, the ERG states that "propensity score matching (albeit a robust method) was based on an outcome *of limited clinical value* not defined in the final NICE scope, namely progression-free survival."	We would request for the wording "*of limited clinical value*" to be removed from the description.	The stated point of "limited clinical value" is not discussed any further as part of the report, and additional argumentation around the importance of PFS as outcome of interest was also provided during the clarification questions (as mentioned by the ERG; page 75).	Not a factual inaccuracy.
Page 22: The ERG report states that "*Furthermore, the analysis was based on PFS, an outcome not specified in the NICE final scope.*"	This sentence should be removed as additional propensity score analyses *based on annual growth rates of target PN (absolute or relative change in target PN volume) and Objective Response Rate* have been provided as part of the clarification questions (A10 a) and b)).	The proposed amendment more accurately reflects the evidence provided over the course of the submission process.	Changed accordingly.

Page 43: The ERG report states that "analyses were based on the PFS data reported in the SPRINT clinical study report (CSR) rather than data from Gross et al. 2020 *as it presented the longest duration of clinical outcome follow-up data*."	This sentence should be updated in line with the explanation provided during clarification questions, stating that "data from the Gross et al. 2020 publication (DCO 29th March 2019) could not be used for the propensity score analyses, *as the validated efficacy dataset, including the individual patient data required for the analyses, is not available to AstraZeneca*."	The suggested amendment provides a more accurate description of the propensity score analyses.	Changed accordingly.
Page 43: The ERG reports that "a small number of patients (n=7) who were included in the Natural History age-matched cohort were subsequently enrolled in *SPRINT* […]."	This sentence should be updated to state "SPRINT Phase II Stratum I" (in line with the corresponding description in Figure 4.1).	The suggested amendment provides a more precise description of the propensity score analyses.	Changed accordingly.

Issue 5 Reporting of airway function

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 70: The ERG report states that "*R_5 is not included in the SPRINT CSR as an assessment for airway function*."	The sentence should be updated to "R_5 is not included in the SPRINT CSR, *however, it is reported by Gross et al. 2020* as an assessment for airway function."	The proposed amendment provides more accuracy on available data for airway function and where this is reported.	Not a factual inaccuracy.

Issue 6 Reporting of pain outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 71: The ERG report states that "[…] there was still *a significant number of* patients	We would suggest removing the mention of "*significant*" and changing the wording to say that "there were still *some* patients	In the absence of a corresponding formal statistical test, the proposed amendment avoids any possible	Changed accordingly.

experiencing deterioration or no change in pain intensity or interference with daily functioning.”	experiencing […].”	misunderstandings regarding the statistical significance of the data presented.	

Issue 7 Inaccurate reporting of numerical data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 67: The ERG reports the adjusted mean (95% CI) pre-cycle 13 change from baseline for NRS-11 as [redacted]. Please note the correct value is [redacted].	Replace [redacted] with [redacted].	The proposed amendment corrects an inaccuracy in the data reporting.	Changed accordingly.
Page 68: The ERG report states the sample size for PedsQL results (parent-reported) to be [redacted]. Please note the correct value is [redacted].	Replace [redacted] with [redacted].	The proposed amendment corrects an inaccuracy in the data reporting.	Changed accordingly.
Page 116, Page 141: The ERG reports the base case incremental QALYs accrued by selumetinib compared to BSC are [redacted]. Please note the correct value is [redacted].	Replace [redacted] with [redacted].	The proposed amendment corrects an inaccuracy in the data reporting.	Changed accordingly.

Issue 8 Inaccurate reporting of published data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 26: The ERG report states that "PN primarily affect the paraspinal region (31%), head and neck (31%) and extremities (*24%*) and […]."	The prevalence of PN which affect the extremities should be corrected to *25%*.	The proposed amendment corrects an inaccuracy in the data reporting.	Changed accordingly.
Page 29: The ERG report states that "pain was identified as a PN-associated symptom in 30% to 41% of patients within two studies, *primarily* resulting from contact with or pressure applied to the PN."	This statement should be changed to "[…] *most commonly* resulting from contact with or pressure applied to the PN."	The proposed amendment more accurately reflects the published data.	Changed accordingly.

Issue 9 Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
Page 71 (Section 4.2.4.1.8)	Missing AiC marking for PII (target tumour pain interference) scores (to be aligned with corresponding marking in the company submission, page 110).	"There was a [redacted]."	Changed accordingly.

Page 73 (Table 4.16)	Missing AiC marking for the probability of remaining progression free at 2 years (to be aligned with the corresponding marking in the company submission, page 99).	"To allow for comparison to the placebo arm of the tipifarnib study, these values are based on [redacted] patients with progressive PN in the 18 months prior to enrolment of SPRINT Phase II Stratum I. The text of the CS (page 99) reported this estimate as: [redacted]."	Changed accordingly.
Page 76 (Section 4.2.4.2.1)	Missing AiC marking for adverse event data (to be aligned with the corresponding marking in the company submission, page 121).	"The two most common AEs were [redacted]."	Changed accordingly.