Medicinrådet

Bilag til Medicinrådets anbefaling vedr. selumetinib til behandling af symptomatiske, inoperable pleksiforme neurofibromer hos pædiatriske patienter med neurofibromatose type 1 i alderen 3 år og derover

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. selumetinib
2. Forhandlingsnotat fra Amgros vedr. selumetinib
3. Ansøgers endelige ansøgning vedr. selumetinib

Copenhagen, April 26th, 2024

To Medicinrådet,

Alexion (an AstraZeneca rare disease company) is hereby responding to Medicinrådets (DMC) draft assessment report for "selumetinib til behandling af symptomatiske, inoperable plexiforme neurofibromer hos pædiatriske patienter med neurofibromatose type 1".

Overall, we find the DMC report to be balanced and thorough. The report concludes that there is a high unmet medical need, no approved treatment options for this rather small patient population of children diagnosed with neurofibromatosis type 1 (NF1)- Plexiform Neurofibroma (PN).

In this response, we are stressing three key points that we ask to be taken into account when deciding if to grant selumetinib positive recommendation at the DMC meeting on May 22nd, 2024:

1. Treatment initiation and length of treatment

Selumetinib is a selective, mitogen-activated protein kinase ½ inhibitor used to treat inoperable and symptomatic PNs in patients with NF1, a rare genetic condition. PN are non-malignant peripheral nerve sheath tumours, which can occur anywhere in the body and cause substantial morbidities.

In the Danish setting, the mean age of diagnosis of the first PN is 6,3 years of age[1]. Expert opinion (Nordic advisory board) suggests that treatment with selumetinib should be initiated as early as possible, on average 2 years after diagnosis. As such, the most clinically relevant start age in the model is 8,3 years (as compared to 10,2 years in the DMC report and 6,3 in the initial application by AstraZeneca).

Selumetinib is not intended for chronic use. From the regulatory phase 2 study SPRINT, 48% of children included in the study had discontinued treatment after 48 months. This is in line with expert opinion from advisory board where clinicians state that treatment should be maintained while benefits remain. The decision to stop treatment should be based on physician decision in close dialogue with the child and family. The model allows for capping the treatment at a certain age (by ticking "include treatment duration cap"). In the submitted base-case scenario this box was not selected. Including a treatment cap at age 18, will significantly reduce the ICER.

2. Size of the treatable patient population

NF1-PN is a heterogeneous, rare and debilitating disease. It is difficult to accurately estimate the number of patients eligible to treatment with selumetinib. Alexion did in the application estimate between 23-25 patients in year 1. Based on the feedback from medical experts, local publications, and information from the ongoing early access program, aligned with DMCs assessment on page 15 in the report, we believe that the number might be overestimated. More likely, approximately 15-20 children will be treated with selumetinib in year 1 if selumetinib receives a positive recommendation (with two new patients per year). Important again to stress is that selumetinib is not intended for chronic use and data from the SPRINT study suggest that after 4 years 48% children have stopped treatment. Thus, the patient population is not expected to expand over time.

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3. Assessing the health-related quality of life

NF1-PN is a serious and debilitating disease, severity affecting the quality of life of the child and the family. We acknowledge the difficulty to estimate the utilities associated with the different health states in the model. Children affected with severe illness tend to adapt to their situation ("coping"), which is well documented; thus, making it even more difficult to estimate the consequence of disease on health-related quality of life. In our model, we have used data from a vignette study, which is recommended in ISPOR guidelines.

The DMC refer to data from a Canadian study. We would like to stress that only 39% of patients had known PN and it was not specified if inoperable. As such the population in the Canadian study does not have the same severity of disease and is not comparable to the population eligible for treatment with selumetinib.

Administration of selumetinib:

We would also like to make DMC aware of a recent SmPC update in October 2023[2]. The administration section now reads: "Koselugo er til oral brug. Det kan tages med eller uden mad (se pkt. 5.2)". Therefore, we ask DMC to remove the sentences/sections in the report referring to language such as "Patienten skal være fastende 2 timer før og 1 time efter doseringen" (page 4 and 14).

We are further improving the administration of selumetinib for the youngest children with a new granular formulation aimed for use in children (2-7 years of age) who might find it difficult to swallow capsules. This new formulation is estimated to obtain EMA approval in 2025.

Selumetinib was granted orphan designation on 31 July 2018 and there are currently no approved treatment options available. As described in the DMC report and in Ejerskov et al 2023, early treatment initiation is key to secure the benefits.

In addition, SPRINT data and expert opinion suggest that the selumetinib is not a chronic treatment. Importantly, there is a window of opportunity to reduce the tumour growth during the phase when children are growing rapidly.

Early initiation improves the cost effectiveness of selumetinib treatment thus resulting in a an ICER within the range to be considered cost-effective.

Kind regards,

Anya Brandt and Karin Brännvall
Alexion Pharma Nordics

References:

1) Ejerskov et al 2023. Clinical Characteristics and Management of Children and Adults with Neurofibromatosis Type 1 and Plexiform Neurofibromas in Denmark: A Nationwide Study. Oncol Ther 2023 Mar;11(1):97-110
2) https://www.ema.europa.eu/da/documents/product-information/koselugo-epar-product-information_da.pdf

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25.04.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.05.2024
Leverandør	Alexion
Lægemiddel	Koselugo (selumetinib)
Ansøgt indikation	Selumetinib er indiceret som monoterapi til behandling af symptomatiske, inoperable plexiforme neurofibromer (PN) hos pædiatriske patienter med neurofibromatose type 1 (NF1) i alderen 3 år og derover.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Koselugo (selumetinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Koselugo (selumetinib)	10 mg	60 stk.	35.708	[redacted]	[redacted]
Koselugo (selumetinib)	25 mg	60 stk.	89.270	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har indgået en aftale med leverandøren som gælder fra den 23.05.2024. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen godkendt behandling til patienter med symptomatiske, inoperable plexiforme neurofibromer. Tabel 2 viser lægemiddeludgiften pr. patient for et års behandling med en dosis på 30 mg 2 gange dagligt – dette svarer til en patient på 10,2 år med en legemsoverflade (BSA) på 1,24 m^2, jf. Medicinrådets antagelse om tidspunkt for behandlingsstart.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Koselugo	10 mg	60 stk.	30 mg to gange dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted] Den tilbudte pris er ikke betinget af Medicinrådets anbefaling.

Medicinrådet

Application for the assessment of Koselugo® (selumetinib) for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

Submitted May 20th ,2022
1st validation received September 19th ,2022
Updated application submitted November 2nd ,2022
2nd validation received March 31st, 2023
Updated June 7th, 2023
Updated February the 18th, 2024

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Koselugo®
Generic name	Selumetinib
Marketing authorization holder in Denmark	AstraZeneca AB, SE 151 85 Södertälje Sweden
ATC code	L01EE04
Pharmacotherapeutic group	Antineoplastic agents, protein kinase inhibitor
Active substance(s)	Selumetinib
Pharmaceutical form(s)	Hard capsule

Overview of the pharmaceutical	
Mechanism of action	Selumetinib treatment for NF1 PN opposes the effects of NF1 mutations by inhibiting MEK1/2 [1], downstream effectors of RAS required for the cell proliferation and survival [2-4]. Therefore it prevents abnormal growth by reducing cell proliferation and preventing abnormal cell survival. In this way, selumetinib can prevent PN growth and promote tumour shrinkage.
Dosage regimen	Selumetinib is administered twice daily at a dose of 25 mg/m^2 of body surface area (BSA), up to a maximum single dose of 50 mg. The dose is rounded to the nearest achievable 5 mg or 10 mg dose [5].
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above [5].
Other approved therapeutic indications	Not applicable
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	Hard capsules, 60 units, 10 mg Hard capsules, 60 units, 25 mg
Orphan drug designation	On 31 July 2018, orphan designation (EU/3/18/2050) was granted by the European Commission to AstraZeneca AB, Sweden, for selumetinib for the treatment of neurofibromatosis type 1 [6]. Following the CHMP positive opinion on this marketing authorization, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Koselugo® as an orphan medicinal product in the approved indication. The COMP recommended Koselugo® (selumetinib), not to be removed from the Community Register of Orphan Medicinal Products [7].

2. Abbreviations

6MWT	Six-minute walk test
90DSU	90-day safety update
ADRs	Adverse drug reactions
AEs	Adverse events
AIC	Akaike information criterion
AIP	Apotekets indkøbspris
AUC	Area under the curve
BIC	Bayesian information criterion
BID	Twice daily
BOR	Best objective response

BSA	Body surface area
BSC	Best supportive care
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMTs	Clinically meaningful thresholds
cPR	Confirmed partial response
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DDK	Danish krona
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
DVQ	Dysfunctional voiding questionnaire
ECG	Electrocardiogram
ECHO	Echocardiogram
GIC	Global impression of change
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
I-NF-DC	International Consensus Group on Neurofibromatosis Diagnostic Criteria
IPTW	Inverse Probability of Treatment Weighting
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MEK 1/2	Mitogen activated protein kinase kinases 1 and 2
MMRM	Mixed model repeated measures
MMT	Manual muscle testing
MPNSTs	Malignant peripheral nerve sheath tumour
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI	National Cancer Institute
NF1	Neurofibromatosis type 1
NH	Natural History
NIR	Near-infrared reflectance
NRS-11	Numerical rating scale 11
LY	Life years
OCT	Optical coherence tomography
ORR	Objective response rate
OWSA	One way sensitivity analysis
PD	Progressed disease

PedsQL	Paediatric quality of life inventory
PFS	Progression-free survival
PII	Pain interference index
PN	Plexiform neurofibromas
PR	Partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RasGAP	Ras-GTPase activating protein
Ras-GTPase	Rat Sarcoma Guanosine triphosphate
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SAEs	Serious adverse events
SD	Standard deviation
SmPC	Summary of product characteristics
SMR	Standardized mortality rate
SoC	Standard of Care
SOC	System organ class
Std. Diff	Absolute standardised difference
TSD	Technical support document
TTP	Time to progression
TTD	Time to discontinuation
TTO	Time-trade-off
uPR	Unconfirmed partial response
VAS	Visual analogue scale

3. Tables and Figures

3.1 Table of tables

3.2 Table of figures

4. Summary

4.1 Koselugo® (selumetinib)

Koselugo® (selumetinib) is a selective, non-ATP-competitive mitogen-activated protein kinase (MEK) 1/2 inhibitor used to treat inoperable and symptomatic Plexiform Neurofibroma (PN) in patients with neurofibromatosis type 1 (NF1), a rare genetic condition. PN are non-malignant peripheral nerve sheath tumours, which can occur anywhere in the body and cause substantial morbidities. Selumetinib is used to control and reduce the volume of PN, and may be given in addition to supportive care in paediatric patients. Currently, the only treatment options for patients with NF1 PN are surgery and best supportive care (BSC). Therefore, the treatment of the condition with selumetinib is highly relevant in the Danish setting.

On the 22nd of April 2021, the CHMP adopted a positive opinion on selumetinib, recommending the granting of a conditional marketing authorization. A marketing authorization valid throughout the European Union was issued on the 17th of June 2021. Moreover, on the 31st of July 2018 the orphan designation (EU/3/18/2050) was granted by the European Commission to AstraZeneca AB, Sweden, for selumetinib for the treatment of neurofibromatosis type 1. The COMP maintained this orphan designation following the CHMP positive opinion.

Selumetinib is administered twice daily (BID) at a dose of 25 mg/m^2 of body surface area (BSA), up to a maximum single dose of 50 mg. The dose is rounded to the nearest achievable 5 mg or 10 mg dose. Treatment with selumetinib should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours, with use of selumetinib restricted to patients with a medical prescription.

4.2 Clinical documentation for selumetinib

The efficacy and safety of selumetinib was evaluated in the single-arm trial SPRINT (NCT01362803), which is the only Phase I/II, trial investigating selumetinib in paediatric NF1 patients with inoperable PN.

Overall, all evaluable patients receiving selumetinib (96%; 48/50) experienced either a meaningful reduction in PN volume or disease stabilisation. A total of 22% (11/50) of patients receiving selumetinib in SPRINT Phase II Stratum I experienced stabilisation of their disease, 6% of patients (3/50) had an unconfirmed partial response, and no patients receiving selumetinib had PN growth >20% (defined as disease progression). The stabilisation of the disease at an early stage of development in the paediatric setting is an outcome of high relevance, highlighting the effectiveness of the treatment in the targeted population.

The majority of children enrolled in the SPRINT trial (latest DCO), 68% (34/50), had a confirmed partial response to selumetinib treatment, representing a ≥20% reduction in target PN volume from baseline, the primary endpoint in the study used to evaluate the efficacy of the treatment. Therefore, selumetinib benefits patients through the reduction in volume of symptomatic PN, which does not generally occur in the absence of disease-modifying treatment. Moreover, once PN-related symptoms such as disfigurement, pain and physical impairment develop, they are extremely unlikely to resolve spontaneously [8].

Other important secondary endpoint highlighted in the study was the progression free survival (PFS); after three years follow-up, 84% of patients in SPRINT remained progression-free, compared with only 15% in the Natural History age-matched cohort used as indirect comparison. Therefore, selumetinib prevents PN volume growth and disease progression.

Selumetinib demonstrated a generally predictable and manageable safety profile in paediatric patients with symptomatic, inoperable NF1 PN and would be suitable for long-term treatment.

4.3 Health economic analysis

The most relevant comparator considered for the analysis in Denmark consist of BSC, which is the only treatment recommended by the Danish guidelines. The base case of the cost-utility analysis reflects this, comparing selumetinib in combination with BSC to BSC only, which is assumed to represent negligible costs, in a Danish setting from a restricted societal perspective. The analysis was performed using a 100 years-time horizon and costs and benefits were discounted with 3.5%, 2.5% and 1.5% according to the year thresholds recommended by the Danish Ministry of Finance.

The cost-utility analysis predicted that selumetinib in combination with BSC was more effective and more costly than BSC alone, with an incremental cost-effectiveness ratio (ICER) of DKK 1,728,474.

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5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

Neurofibromatosis type 1 (NF1) is a cancer predisposition syndrome. The inheritance of such condition follows an autosomal dominant trait, but in approximately 50% of the patients the syndrome is caused by a *de novo* mutation [9], which may delay the diagnosis especially in children. The NF1 gene underlying the syndrome is located on chromosome 17 and encodes neurofibromin tumour suppressor protein. Neurofibromin functions as a Ras-GTPase activating protein (RasGAP), and NF1 mutations lead to over-activation of the Ras signalling pathway [10]. The relative risk of cancer among patients with NF1 is the highest in childhood and adolescence. Moreover, paediatric patients with NF1 have a substantial risk of developing tumours in the central nervous system, with a higher cancer standardized incidence rate among females than males [10].

5.1.1 Neurofibromatosis

NF1 is a rare, complex, lifelong, and incurable genetic disease with many of its symptoms arising in early childhood and continuing into adulthood. NF1 is caused by mutations in the tumour suppressor gene neurofibromin 1 [11-14]. The disease does not show any association with gender or ethnicity [15].

NF1 is a highly heterogeneous disease, that can express differently between patients, and even between family members with identical mutations [16-18]. NF1 can present a wide range of clinical manifestations involving multiple organ systems, with symptoms affecting the nervous system, skin, bones, and eyes [19-22]. Therefore, NF1 patients require multidisciplinary care from a range of medical professionals. For the majority of NF1 patients the clinical course of the disease is uncertain, necessitating regular monitoring for new manifestations [23]. The uncertainty surrounding the disease course can be a source of anxiety for both patients and their families or carers, severely impacting their quality of life [24, 25].

The majority of NF1 patients (80–85%) are diagnosed by the age of six, and by the age of eight years, almost all NF1 patients (95%) will have been diagnosed [26, 27]. The diagnostic criteria were revised by an international consensus panel of neurofibromatosis experts with updated criteria published in 2021 (Table 1) [28]. The diagnostic criteria are met, in an individual who does not have a parent diagnosed with NF1, if two or more of the criteria are present. In a child of a parent diagnosed with NF1 the diagnostic criteria are met if one or more of the criterion are present [28].

Table 1. International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC) diagnostic criteria for NF1

Category	I-NF-DC NF1 diagnostic criteria
Clinical presentation	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.

Category	I-NF-DC NF1 diagnostic criteria
	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.

[a]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally 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.

5.1.1.1 Plexiform neurofibroma

One of the more severe clinical manifestations of NF1 is plexiform neurofibroma (PN), which occurs in 30-50% of NF1 patients [29-32]. 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 [8]. 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%) [29, 33, 34].

Magnetic resonance imaging (MRI) is the standard imaging modality for the diagnosis of PN. Around 30% of NF1 patients have visible PN, which may be diagnosed when they first appear or be identified following annual routine physical examinations. However, approximately 20% of NF1 patients present with internal PN, which can only be identified through imaging [20, 32, 35]. Internal PN may have overlying skin manifestations, such as discoloration, which aid diagnosis [36]. NF1 patients who experience new neurological symptoms, such as focal limb weakness or sensory changes, should undergo MRI to evaluate whether PN are present [36, 37].

PN grows rapidly in children younger than 18 years old, with volume increases reaching ≥20% per year [38, 39]. The most rapid PN growth rates are found in patients aged 3–5 years, with a median growth rate of 35% per year observed in this age group [8]. In adulthood, PN growth rates tend to reduce and plateau [38, 39]. PN growth is frequently uncontrolled and unpredictable, and patients may experience periods of rapid growth followed by periods of inactivity [8, 20]. As the most rapid growth of PN is observed in young children, the early diagnosis and treatment of NF1 PN patients is fundamental [40].

As PN grows, PN-associated morbidities may develop such as pain, disfigurement, motor dysfunction, visual dysfunction and, in the most severe cases, life-threatening complications such as respiratory impairment [8]. In the most serious cases, PN can lead to significant disability (for example by placing pressure on spinal nerves) and can be life-threatening, (for example through the obstruction of airways) [24, 33, 41].
The number and severity of PN-associated morbidities is correlated with volume increases [40]. PN rarely decrease in volume spontaneously in the absence of efficacious treatment and consequently, PN-related symptoms are also extremely unlikely to resolve spontaneously [8]. This results in a lifelong clinical and HRQoL burden for NF1 PN patients [8, 39, 42]. Hence, there is a clear need for a treatment option which can reduce PN volume and PN-associated morbidities and burden, thereby improving patient and caregiver QoL.

PN grow around, within or near critical structures and are highly vascularised. As such, they present many difficulties in terms of surgical resection. Proximity to vital structures and the extent of vascularisation are two important factors used to determine the extent to which resection of a PN can be performed. In terms of surgical resection, PN can be divided into three categories [43]:

- PN which can be completely removed by surgery (completely resectable).
- PN which can be partly removed by surgery, with the proximity to critical structures often limiting the extent of removal (partially resectable).
- PN which cannot be removed due to the risks associated with their location and vascularisation (not resectable).

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, with the estimated rate of recurrence ranging from 29 – 45% of cases [43]. Even PN which have been completely resected may recur in paediatric patients in up to 20% of cases [33, 43, 44]. A PN is considered inoperable when it cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity [43].

PN can be further classified into symptomatic or asymptomatic, depending on whether patients experience PN-associated morbidities or not. Patients with symptomatic NF1 PN experience the morbidities associated with their PN in addition to the clinical manifestations associated with NF1 [33, 44, 45].

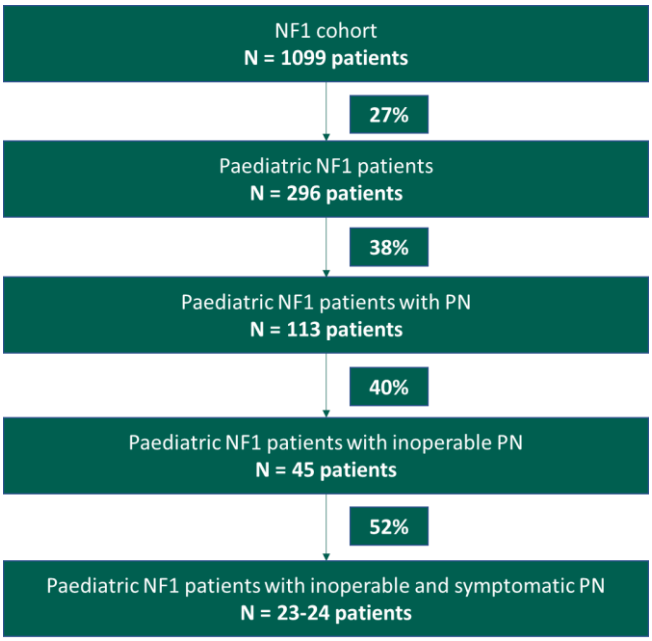
The average life expectancy in NF1 is reduced by approximately 8–15 years [35, 46, 47]. This reduction in life expectancy is primarily due to malignancies. NF1 patients also have an increased lifetime risk of developing certain forms of cancer, including malignant peripheral nerve sheath tumour (MPNSTs), brain tumours, gastrointestinal stromal tumours, breast cancer and leukaemia [15]. In addition to PN-associated morbidities, some studies have indicated a higher mortality rate for NF1 PN patients than for the general NF1 population [48], with the risk of developing an MPNST being increased 20-fold in an area with an existing PN [49]. Additionally, having a symptomatic PN has been shown to influence the mortality rate (mortality rate increased by 3.2% for patients with symptomatic PN compared with no PN or asymptomatic PN [p=0.024]) [33]. Moreover, people with symptomatic NF1 PN experience the morbidities associated with their PN in addition to the clinical manifestations associated with NF1, such as attention deficit hyperactivity disorder, autism and anxiety and depression.

5.1.2 Patient population in Denmark

A nationwide, longitudinal cohort study of Danish patients with NF1, with or without PN, was conducted between 1st January 2000 and 1st July 2020 at the two national centres of NF1 expertise (the Centre for Rare Diseases in Aarhus [AUH-CRD] and in Copenhagen [CPD-CRD]). In the study, patients with NF1 were monitored throughout their lifetime, regardless of disease severity [50]. This cohort was composed by 1,099 NF1 patients; out of these 1,099 patients, 296 were paediatric (aged ≤ 17 years) and 113 of these 296 paediatric patients had NF1 with PN [50].
The Danish national cohort study presents detailed statistics for those patients having a PN larger than 3 cm with respect to inoperability and symptomatic PN [50]. Assuming that these statistics apply for the larger sample (regardless of PN size), it is possible to estimate the number of patients eligible for treatment with selumetinib in Denmark. Among the 113 patients with NF1 and PN, 40% will present with an inoperable PN, accounting for 45 patients [50]. The mean age of the patients at NF1 diagnosis was 4 years [50].
Additionally, 52% of patients in the inoperable, large PN cohort had a symptomatic PN [50]. Therefore, by using the same proportion, the total number of NF1 patients with inoperable and symptomatic PN is approximately 23, corresponding to 2.13% of the original NF1 cohort of 1099 patients. Consequently, in July 2020, there were approximately 23 alive paediatric NF1 patients with symptomatic and inoperable PN in Denmark.

Accordingly, and accounting for the uncertainty around the assumptions, the expected prevalent population to be eligible for treatment with selumetinib in Denmark is around 23 patients (Figure 1). The incidence was calculated by dividing the prevalent population (23 patients) by the age span of the indication of selumetinib (3-18 years old). This results in approximately 2 new patients eligible for treatment with selumetinib each year in Denmark.

Figure 1. Prevalent patients eligible for treatment with selumetinib in Denmark



Therefore, the incidence of symptomatic, inoperable NF1 PN in the Danish population is 2 in approximately 5 million and the prevalence is 23 in approximately 5 million. The incidence and prevalence in the Danish population, over 5 years, expressed for 100,000 habitants are presented in Table 2, while the estimated number of patients eligible for treatment by year is presented in Table 3. The incidence and prevalence values per 100,000 inhabitants were calculated using the incidence and prevalence results obtained from the longitudinal cohort study of Danish patients with NF1 and the Danish total population figures taken from the national Danish statistics from 2017 to 2021. The incidence and prevalence over 5 years are assumed to be constant.

Table 2. Incidence and prevalence for 100,000 habitants in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	0.0348 (2 patients)	0.0346 (2 patients)	0.0344 (2 patients)	0.0344(2 patients)	0.0342 (2 patients)
Prevalence in Denmark	0.400 (23 patients)	0.397 (23 patients)	0.395 (23 patients)	0.395 (23 patients)	0.393 (23 patients)
Global prevalence	0.426 in 100,000	0.426 in 100,000	0.426 in 100,000	0.426 in 100,000	0.426 in 100,000

It was also possible to make an estimation of the European prevalence of symptomatic, inoperable NF1 PN. In Europe, the prevalence of NF1 is around 20 patients every 100,000 inhabitants [51]. If we assume that the proportions observed

in the Danish cohort are also valid for Europe, approximately 2.13%[1] of the original cohort with NF1 in Europe would have NF1 with inoperable and symptomatic PN in a paediatric age. Therefore, out of the starting 20 patients every 100,000 inhabitants, only 0.426 patients in 100,000 people will have inoperable, symptomatic, NF1 PN in a paediatric age in Europe (Figure 2).

Figure 2. Estimated European prevalence using Danish proportions

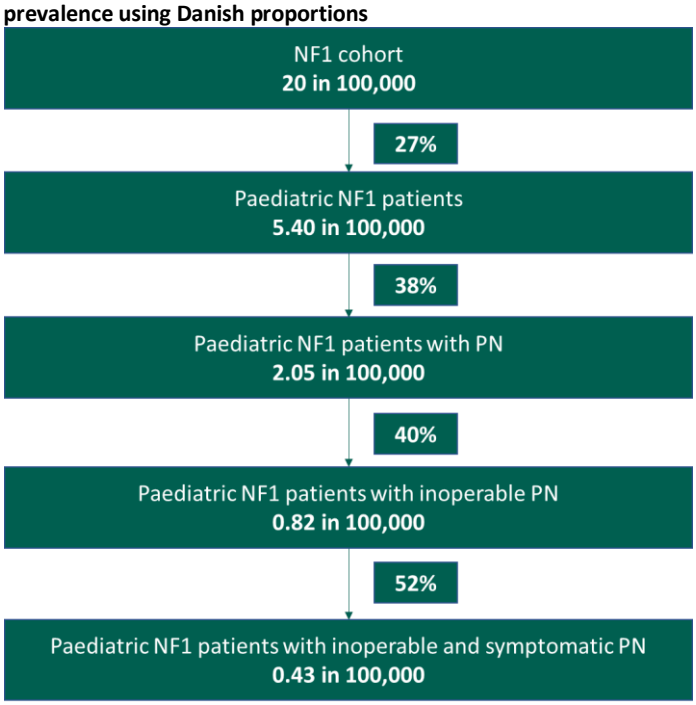


Table 3. Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to be eligible for treatment with selumetinib in the coming years	25	27	29	31	33

5.1.3 Patient populations relevant for this application

The relevant patient population that is expected to use selumetinib is in line with the indication of selumetinib issued by the European Medicines Agency (EMA) i.e. paediatric patients with NF1 and symptomatic, inoperable PN aged 3 years and above, with NF1 and symptomatic, inoperable PN. A PN is considered inoperable when it cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity. In order to represent the Danish population, the health economic analysis will refer to the patients enrolled in the cohort study of Danish patients with NF1. According to Danish clinical practice, the indication of the therapy is rather flexible therefore patients' needs would be identified by the clinical expert [52].

Furter details concerning the baseline characteristics of the population included in the health economic analysis are shown in Section 8.2.2.1 and in Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety. The trial population selected through the clinical criteria used in SPRINT properly reflected the Danish patient population according to a Danish clinical expert [52]. According to the Danish clinical

[1] Using the Danish proportion, the number is obtained through following calculations: 27% (296/1099) are pediatric, 38% (113/296) develop PN, 40% (14/35) will be inoperable and out of them 52% will have the symptomatic PN = 27%*38%*40%*52% yields 2.13%. Note: the 40% and 52% proportions were derived from patients having a ≥ 3 cm larger PN in the Danish cohort study.

practice, the location of the tumour would influence the type of function it impacts, and it would be considered as a relevant clinical criterion to start the treatment. The patients will be selected according to the following criteria [52]:

- Significant tumour that impacts the patient in function or QoL
- Dependent on location and age
- Located in an area where if there is growth in the future it could cause deformation or significantly impact function, for e.g. face, head, neck, throat, spine, thorax, abdomen.
    - In the literature tumours significantly affecting limb, like arm or leg, have also been described as invasive.
    - If the tumour is peripherally located, e.g. near the skin, the preference would be to operate than to take a medication twice daily.
- Large tumour burden – individual tumour may not be big, but there might be many tumours. One may speculate whether there is a greater risk of malignancy.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

There are currently no international guidelines specifically for the treatment and management of NF1 PN, which reflects the lack of efficacious non-surgical treatments. It is recommended that both paediatric and adult patients with NF1 PN undergo regular monitoring, through a specialist service if possible [20, 36, 37, 53, 54]. Treatment plans are based on the individual patient's needs and clinical presentation [20, 53].

In Denmark, current treatment options are reduced to symptom management and surgery. The only management option for PN which can reduce or remove the tumours is surgery. Nonetheless, surgery is often complicated given the localization of PN, their high vascularization [55], and the high risk of complications including life-threatening haemorrhage, delayed wound healing, pain, functional deficits, permanent neurological deficits, disfigurement, palsy and airway obstruction [33, 44, 56]. As a result, only partial resection is achieved in many patients, and PN that have only been partially resected often recur and regrow in paediatric patients and continue to cause morbidities (29 – 45% of cases) [33, 43]. Even PN which have been completely resected may recur in paediatric patients in up to 20% of cases [33, 43, 44]. As a result, most patients with NF1 PN (>80%) are considered inoperable as the PN cannot be completely surgically resected without risk of substantial morbidity [8, 20, 33, 43, 44, 56].
In such cases, the only option is palliative care or symptomatic management, such as pain medication, or interventions to alleviate morbidities [8, 57, 58]. Patients may require multiple pain medications, with the number of required medications often increasing as PN grows [8]. However, despite these medications, many patients still report pain interference with everyday life [57]. Consequently, the established symptomatic clinical management often does not control NF1 PN-associated pain sufficiently [8]. Additionally, long-term pain medication, particularly opioids, have multiple adverse effects such as risks of substance abuse, addiction, bone fracture and cardiovascular events [59]. The established symptomatic clinical management for PN-associated morbidities is described in Table 4.

Table 4. Established clinical management for PN-associated morbidities

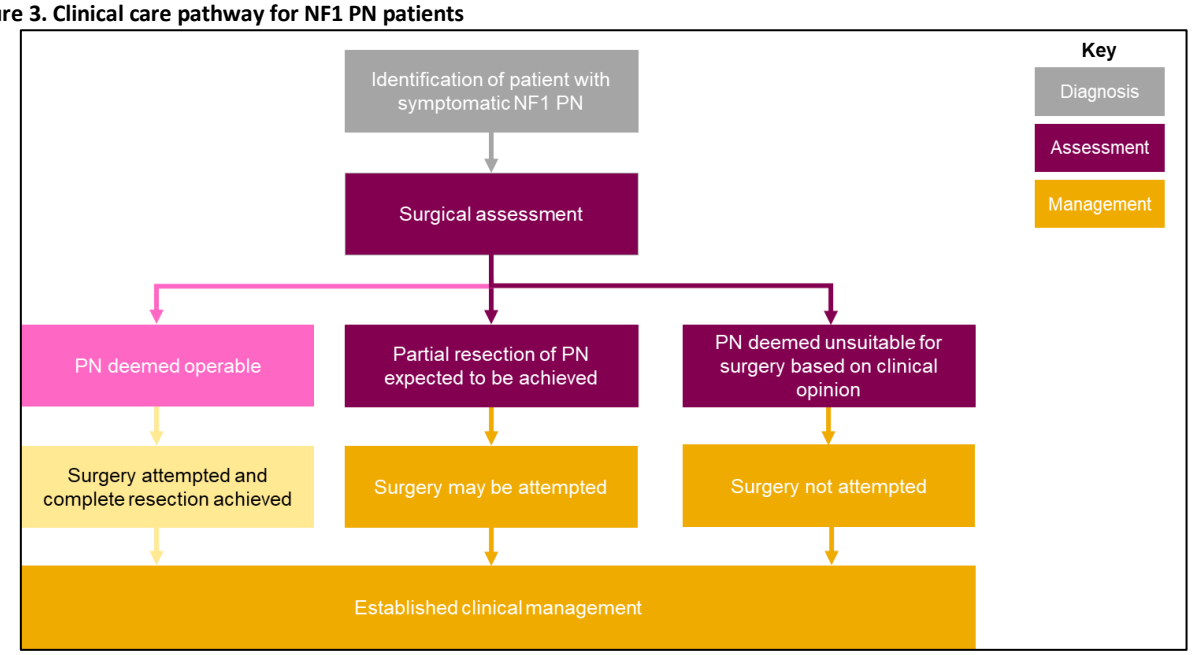
PN-associated morbidity	Established clinical management for PN-associated morbidities
Pain	• Multiple pain medications including scheduled, neuropathic, and opioid pain medications [8]. • Physical therapy may be beneficial [37].

Motor	• Due to significant muscle weakness and disability, the patient may require use of a wheelchair or assistive devices [24]. • Physical therapy may be beneficial [37].
Airway	• Airway obstruction requires patients to undergo tracheostomies [60]. • Airway PN can cause morbidities such as sleep apnoea which may be treated with continuous positive airway pressure [58, 61].
Bladder and bowel	Management of PN-associated bladder morbidities follows the general management for bladder problems [62, 63]: • 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 [64]: • 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 non-surgically, for example in cases of eye misalignment (strabismus) caused by PN restricting eye movement [65]. • 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 [65].

Currently, there are no approved pharmacological treatments that can stabilise or reduce tumour volume in patients with symptomatic, inoperable NF1 PN. Danish guidelines also highlight the complexity of surgery due to the location, close to nerves and other tissues, and the high vascularization of PN [66, 67]. Therefore, patients with symptomatic and inoperable NF1 PN in Denmark are left without any disease-modifying treatment alternatives. This results in increasing PN volume and increasing significant and severe morbidity, which results in an increasing, lifelong burden on patients and their carers [8, 42, 57]. Consequently, there exists a substantial unmet need for an effective treatment to stabilise or reduce PN volume and PN-associated morbidities in patients with symptomatic inoperable NF1 PN in Denmark.

Below in Figure 3 the current care pathway for patients with NF1 PN is illustrated, from NF1 diagnosis to treatment of PN. The following pathway reflects the Danish clinical practice.

Figure 3. Clinical care pathway for NF1 PN patients



Source: [20, 68].

5.2.2 Choice of comparator

In Denmark, there is currently no specific medical treatment for NF1 PN. Treatment with traditional antineoplastic agents such as radiotherapy and chemotherapy is unsuitable due to the risk of PN malignant transformation [69].

Given the lack of treatment options beside surgery and symptom management, the most appropriate choice of comparator for the analysis is BSC, consisting of symptomatic treatment (e.g., analgesics to manage pain) or surgical treatment to remove or reduce the size of the PN, as described in Section 5.2.1. Selumetinib is expected to be used in addition to BSC, which is the current standard of care (SoC). Danish clinical expert considered it a reasonable assumption that patients will routinely see healthcare professionals to assess/monitor NF1, and that patients will also receive treatment for PN symptoms. Since selumetinib is provided in addition to BSC, no cost differential was considered reasonable [52].

5.2.3 Description of the comparator

Given the wide range of PN-related symptoms, the nature of BSC varies quite substantially. Moreover, as a patient's inoperable PN develops and the symptoms progress, symptomatic treatments may become increasingly ineffective.

5.2.4 The Intervention

On 31 July 2018, orphan designation (EU/3/18/2050) was granted by the European Commission to AstraZeneca AB, Sweden, for selumetinib for the treatment of neurofibromatosis type 1 [6]. On 22 April 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorization for the medicinal product Koselugo® [70]. The European Commission granted marketing authorization for Koselugo® on the 17th of June 2021. The information in this section is based on the published Summary of Product Characteristics (SmPC) by EMA [5], if not referenced to another source.

Koselugo® (selumetinib) is an orally available, potent, and selective, non-ATP-competitive mitogen-activated protein kinase (MEK) 1/2 inhibitor which aims to control and reduce the volume of PN. Selumetinib blocks MEK activity and the RAF-MEK-ERK pathway. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.The recommended dose of selumetinib is 25 mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours). Dosing is individualised based on BSA (mg/m^2) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of selumetinib hard capsules can be combined to attain the desired dose as shown in Table 5.
Treatment with selumetinib should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours, with use of selumetinib restricted to patients with a medical prescription. Treatment should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. Clinical benefit is to be determined by the clinicians and it is assessed on the individual patient: this would include symptom improvement, shrinkage or stabilization of tumour, in the absence of unacceptable toxicity [52]. There is limited data in patients older than 18, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician. However, start of treatment with selumetinib in adults is currently not considered appropriate. Moreover, the clinical evidence suggests that stopping criteria for adulthood is consistent with the observed natural history of the disease. Treatment is recommended to be continued as long as the patient experiences clinical benefits and no unacceptable toxicity [52].

Table 5. Recommended dose based on body surface area

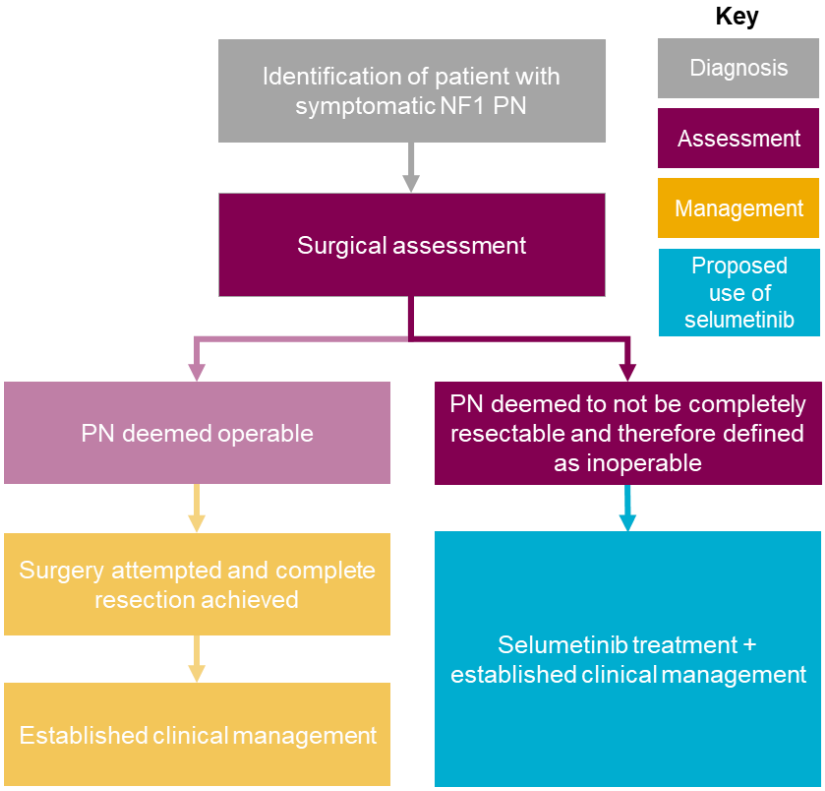
Body surface area (BSA)[a]	Recommended dose
0.55 – 0.69 m^2	20 mg in the morning and 10 mg in the evening
0.70 – 0.89 m^2	20 mg twice daily
0.90 – 1.09 m^2	25 mg twice daily
1.10 – 1.29 m^2	30 mg twice daily
1.30 – 1.49 m^2	35 mg twice daily
1.50 – 1.69 m^2	40 mg twice daily
1.70 – 1.89 m^2	45 mg twice daily
≥ 1.90 m^2	50 mg twice daily

[a] The recommended dose for patients with a BSA less than 0.55 m^2 has not been established.

The population indicated for treatment with selumetinib are paediatric patients 3 years and older with NF1 and symptomatic, inoperable PN. A PN is considered inoperable when it cannot be completely resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity. As described in section 5.2.1, these patients have a high unmet need as their current treatment and management strategies in Denmark are limited to routine monitoring and symptomatic management, also referred to as established clinical management in this dossier [8, 57, 58]. Therefore, selumetinib offers an alternative to the current SoC in Denmark for paediatric NF1 patients with symptomatic PN, which after surgical assessment is not expected to be completely resectable and is therefore defined as inoperable. These patients may continue to require symptomatic management concomitantly with selumetinib treatment [56, 71].

Figure 4 shows the proposed treatment pathway for patients with NF1 PN following the introduction of selumetinib.

Figure 4. Pathway for the treatment of NF1-related PN with selumetinib



Source: [20, 72]

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A single systematic literature review (SLR) was conducted to identify all published studies concerning the treatment of patients with NF1 and inoperable PN. The inclusion and exclusion criteria for the SLR were defined before conducting the searches and are presented in Table 59 and Table 60 in Appendix A – Literature search for efficacy and safety of intervention and comparator(s). The following searches were performed:

Electronic Databases (search conducted on 26th January 2021 and updated on 7th September 2022)

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 September 6th, 2022)
- Embase (searched via the Ovid SP platform, from 1974 to September 6th, 2022)
- The CDSR and CENTRAL, searched simultaneously via The Cochrane Library Wiley online platform, Issue 9 of 12, September 2022
- The DARE, searched via the University of York CRD platform, Issue 2 of 4, April 2015

Conference searches (search conducted on September 6th, 2022)

A manual search of the following conference proceedings from the last three years (2018–2022) 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 2021 and 2022 (September 2022, Vienna)

- Children's Tumour Foundation NF Conference
    - NF Conference 2019 (September 2019, San Francisco)
    - NF Conference 2020 (June 2020, Philadelphia)
    - NF Conference 2021 (June 2021, Virtual)
    - NF Conference 2022 (June 2022; Philadelphia)

- Joint Global Neurofibromatosis Conference (JGNC) 2018 (November 2018, Paris; this event combined the Children's Tumour 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)
    - ESMO 2021 (December 2021, Virtual)
    - ESMO 2022 (December 2022, Geneva)

- 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)
    - ASCO 2021 (June 2021, Virtual)
    - ASCO 2022 (June 202, Virtual)

- International Symposium on Paediatric Neuro-Oncology (ISPNO)
    - ISPNO 2018 (June–July 2018, Denver)
    - ISPNO 2020 (December 2020, Karuizawa)
    - ISPNO 2022 (June 2022, Hamburg)
- American Society of Paediatric Haematology/Oncology (ASPHO)
    - ASPHO 2018 (May 2018, Pittsburgh)
    - ASPHO 2019 (May 2019, New Orleans)
    - ASPHO 2020 (May 2020, Virtual)
    - ASPHO 2021 (April 2021, Virtual)
    - ASPHO 2022 (June 2022, Pittsburgh)

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 (search conducted on 7th September 2022)
The bibliographies of any relevant SLRs and (N)MAs were manually searched to identify any additional, relevant studies for inclusion.

Supplementary Searches (search conducted on 7th September 202)
In addition to the database and grey literature searching performed, a manual search of materials provided by AstraZeneca was conducted. These materials included:

- A targeted literature review (TLR) conducted in 2019 on NF1 PN clinical studies
- A TLR conducted in 2020 to capture HRQoL instruments in NF1

Clinical Trial Registries (search conducted on 28th January 2021, updated September 2022)
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.

No date limit was applied to the electronic database, ClinicalTrials.gov, bibliography, or validation searches.

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.

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.

For further details on the SLR, see Appendix A – Literature search for efficacy and safety of intervention and comparator(s).

In the SLR update (September 2022), 263 records were retrieved from the electronic database searches, of which 50 were duplicates, meaning 213 novel records were screened at the title/abstract review stage. Of these records, 27 full publications were subsequently screened at full-text review. Following a detailed evaluation of the full texts of these articles, 10 records were identified that met the review inclusion criteria.
Supplementary searching identified an additional 24 records that met the inclusion criteria, meaning that a total of 34 publications reporting on 22 unique studies (18 published and 4 unpublished) were identified reporting the treatment of patients with NF1 and inoperable PN. Of the 22 unique studies, 17 were new trials which had not been identified in the original SLR.

6.2 List of relevant studies

Among the eight unique studies identified by the SLR, SPRINT Phase 2 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, and an European public assessment report was published by EMA on the 13th of October 2021 [5]. This study was also a main source to inform the health economic analysis. An overview of the SPRINT Phase 2 Stratum I study is presented

below in Table 6. For detailed information about the SPRINT trial, see Appendix B – Main characteristics of included studies.

Details of the other seven published studies meeting the pre-defined inclusion criteria of the SLR are presented in Table 60 in Appendix A – Literature search for efficacy and safety of intervention and comparator(s).

The NCI Natural History Study of Patients with NF1 and the Tipifarnib Study 01-C-0222 were not captured within the clinical SLR (as the selection criteria required studies to investigate selumetinib as an intervention). However, due to the importance of the control data from these studies, the have also been included in Table 6.

Table 6. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Gross, A.M., et al., "Selumetinib in Children with Inoperable Plexiform Neurofibromas" New England Journal of Medicine, 2020.	SPRINT	NCT01362803	Start date: September 21, 2011 Estimated primary completion date: January 1, 2025 Estimated study completion date: January 1, 2030
Gross, A.M., et al., "Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1" Neuro Oncol, 2018	NCI Natural History Study of Patients With Neurofibromatosis Type I	NCT00924196	Start date: February 25, 2008 Study is ongoing
Widemann, B.C., 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 Oncol, 2014	Tipifarnib (R115777) Study 01-C-0222	NCT00021541	Start date: July 17, 2001 Completion date: February 19, 2009

7. Efficacy and safety

7.1 Efficacy and safety of selumetinib compared to best supportive care for the treatment of symptomatic, inoperable PN in paediatric patients with NF1.

7.1.1 Relevant studies

For the health economic assessment of selumetinib, the pivotal trial SPRINT in its phase 2, stratum I, represents the most relevant study.

Phase 1 of the SPRINT trial was a multicentre, open label, dose-escalation study designed to determine the maximum tolerated dose of selumetinib as a treatment for children with NF1 PN and to evaluate the pharmacokinetics of selumetinib [73].

A total of 24 children (median age, 10.9 years; range, 3.0 to 18.5) with NF1 and inoperable PN which had the potential to cause significant morbidity received selumetinib in the phase 1 trial. Significant morbidity was defined as (but not limited to) head and neck lesions that could compromise the airway or great vessels, paraspinal lesions that could cause myelopathy brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Patients were selected applying the inclusion and exclusion criteria listed in Appendix B – Main characteristics of included studies. The median tumour volume was 1205 ml (range, 29 to 8744). The 24 patients received selumetinib at three dose levels every 12 hours:

- 12 patients at 20 mg per square meter of body surface area.
- 6 patients at 25 mg per square meter.
- 6 patients at 30 mg per square meter.

They received a median of 30 cycles of 28 days each of selumetinib (range, 6 to 56) and 25 mg per square meter every 12 hours was considered to have an acceptable side-effect profile and was determined to be the maximum long-term tolerated dose.

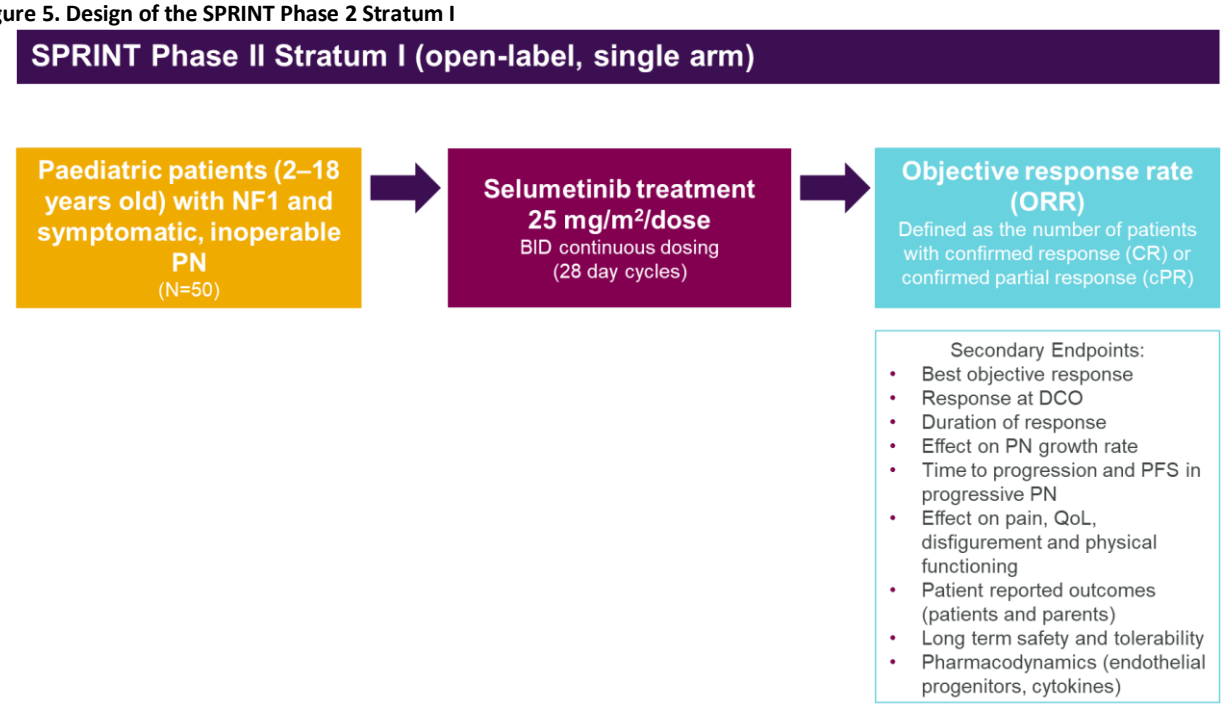
Out of the 24 patients, treatment with selumetinib was discontinued in 5 patients; treatment was stopped because of dose-limiting toxic effects in only 1 of these patients. A decrease from baseline in PN volume was observed in all patients (median change, −31%; range, −5.8 to −47) and 17 of the 24 patients (71%) met the criteria for confirmed partial response (tumour volume decrease from baseline of at least 20% for at least 4 weeks). Partial responses were durable, in that they were sustained for a median of 23 cycles (range, 6 to 42).

Phase 2 of the SPRINT trial was a multicentre, open label study designed to evaluate the response rate to and clinical benefit of selumetinib treatment and included two strata:

- Stratum I includes patients aged 2–18 with NF1 and symptomatic, inoperable PN [42].
- Stratum II includes patients aged 2–18 with NF1 and inoperable PN which have the potential to cause significant morbidity [74].

The SPRINT Phase 2 Stratum I is considered the most relevant study as it investigates 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. Therefore, the focus will be on this study.
Figure 5 illustrates the study design of SPRINT Phase 2 stratum I.

Figure 5. Design of the SPRINT Phase 2 Stratum I



Source: AstraZeneca Data on File (SPRINT protocol),[75] Gross et al. 2020.[42]

In addition to SPRINT, in order to assess the degree of efficacy of selumetinib, an indirect comparison was made with an age-matched cohort within the NCI national history study and with the placebo arm of the tipifarnib Study 01-C-0222. Further details concerning these studies and the baseline characteristics of the patients included in them are presented in Appendix B – Main characteristics of included studies and Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety and in the following section.

7.1.2 Efficacy and safety – SPRINT Phase 2

A total of 50 paediatric patients with NF1 and symptomatic, inoperable PN were enrolled from August 2015 to August 2016 in this interventional, Phase II, open label study conducted in four centres in the US. Selumetinib (25 mg/m^2 BSA BID) was administered in 28-day cycles, with no rest periods between treatment cycles. Evaluations were performed prior to starting a new cycle [42, 75, 76].

The SPRINT Phase 2 Stratum I 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 Section 5.1) and no effective, disease-modifying medical treatment.
- Paediatric patients enrolled on the SPRINT Phase 2 trial had substantial PN-related morbidity at study entry [42]; and
- Phase 1 of the SPRINT trial had demonstrated promising efficacy for selumetinib in this population (ORR 71%) [73].

Therefore, to determine the comparative effectiveness of selumetinib vs established clinical management, several pre-planned, non-randomised comparisons vs external controls were explored [71]:

1. A naïve comparison between SPRINT Phase 2 Stratum I and an age-matched cohort of children with symptomatic inoperable NF1 PN from the NCI NH study [42]. The NCI NH study is a robust observational, longitudinal study of patients with NF1 PN and provides a comprehensive description of the disease course in a relatively large patient cohort [42]. The age-matched cohort was a subset of the full NH study cohort. The cohort included patients aged 3–18 years (median age 7.8 years) who had a least two volumetric MRI scans, with the first scan performed between the ages of 3–18 years (considered baseline). This approach allowed alignment with the age of the enrolled population and the evaluation time of the baseline volumetric scan in the SPRINT Phase 2 Stratum I, to allow for a robust comparison [42, 71]. To directly compare the data in the age-matched cohort to the data from SPRINT Phase 2 Stratum I, a cohort of 93 patients with a maximum duration of follow-up of 3.2 years was selected. This follow-up period was equal to the maximum duration of follow-up in SPRINT Phase 2 Stratum I [42, 71]. Further details concerning the study and the baseline characteristics of the patients are presented in Appendix B – Main characteristics of included studies and Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

   The PN growth data from patients with NF1-related PN in the NH study age-matched cohort was analysed and served as an external control for NF1-related PN growth and PFS data in SPRINT Phase 2 Stratum 1. This external comparison was planned as part of the protocol for SPRINT Phase 2 Stratum I [42, 71].

   In addition to the naïve comparison with the NH study age-matched cohort, propensity score analyses were explored for the non-randomised comparison of progression-free survival (PFS) for selumetinib in the SPRINT Phase 2 Stratum I versus the NH study. These analyses are described in Appendix F – External control: Natural History study propensity score matched analysis

2. A naïve comparison of PFS between SPRINT Phase 2 Stratum I and patients with NF1 and unresectable, progressive PN from the placebo arm of the tipifarnib Study 01-C-0222. This study is a Phase 2 randomised, cross-over, double-blind, placebo-controlled trial that was designed to evaluate the safety and efficacy of the farnesyltransferase inhibitor, tipifarnib, in paediatric patients with NF1 and progressive PN. The trial was designed with a placebo arm, to be used as a historical control for future studies of interventions for NF1 PN [77]. This external comparison was also planned as part of the protocol for SPRINT Phase 2 Stratum I. Further details concerning the baseline characteristics of the tipifarnib placebo arm, where available, are described in Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

   The tipifarnib 01-C0222 study used a cross-over design. Patients were randomised to either the placebo group (n=29) or the tipifarnib group (n=31). In Phase A of the trial, participants were followed on their first 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. PN were assessed using volumetric MRI and progression was

determined by a PN volume increase of ≥20% in at least one PN compared with baseline on Phase A or Phase B [77].

The main characteristics of SPRINT Phase 2 stratum I, are summarized in Table 63 in Appendix B – Main characteristics of included studies. Below are described in detail the efficacy and safety results of the study including the results of the naïve comparisons. For further insights, Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety describes the baseline patient characteristics of the studies and Appendix D – Efficacy and safety results per study defines the endpoints.

7.1.3 Primary efficacy outcome: objective response rate

The primary outcome measure of the SPRINT Phase 2 Stratum I was ORR to selumetinib, defined as the rate of confirmed PR and CR, using volumetric MRI analysis [72].

The majority of children, 68% (34/50), had a cPR to selumetinib treatment, representing a ≥20% reduction in target PN volume from baseline [42]. Most evaluable patients receiving selumetinib (96%) experienced either clinically meaningful PN reduction or disease stabilisation. The ORR was unchanged at the most recent DCO (27th February 2021) and this result was consistent with the finding from the SPRINT Phase 1 trial (cPR of 71%) [73]. In contrast, none of the age-matched patients in the NCI NH study had a ≥20% reduction in tumour volume over the same time period (3 years) [42]. Therefore, selumetinib treatment benefits patients through the reduction in volume of symptomatic PN, which does not generally occur in the absence of disease-modifying treatment [42].

7.1.4 Secondary outcomes: Tumour volumetric responses

7.1.4.1 PN growth rate

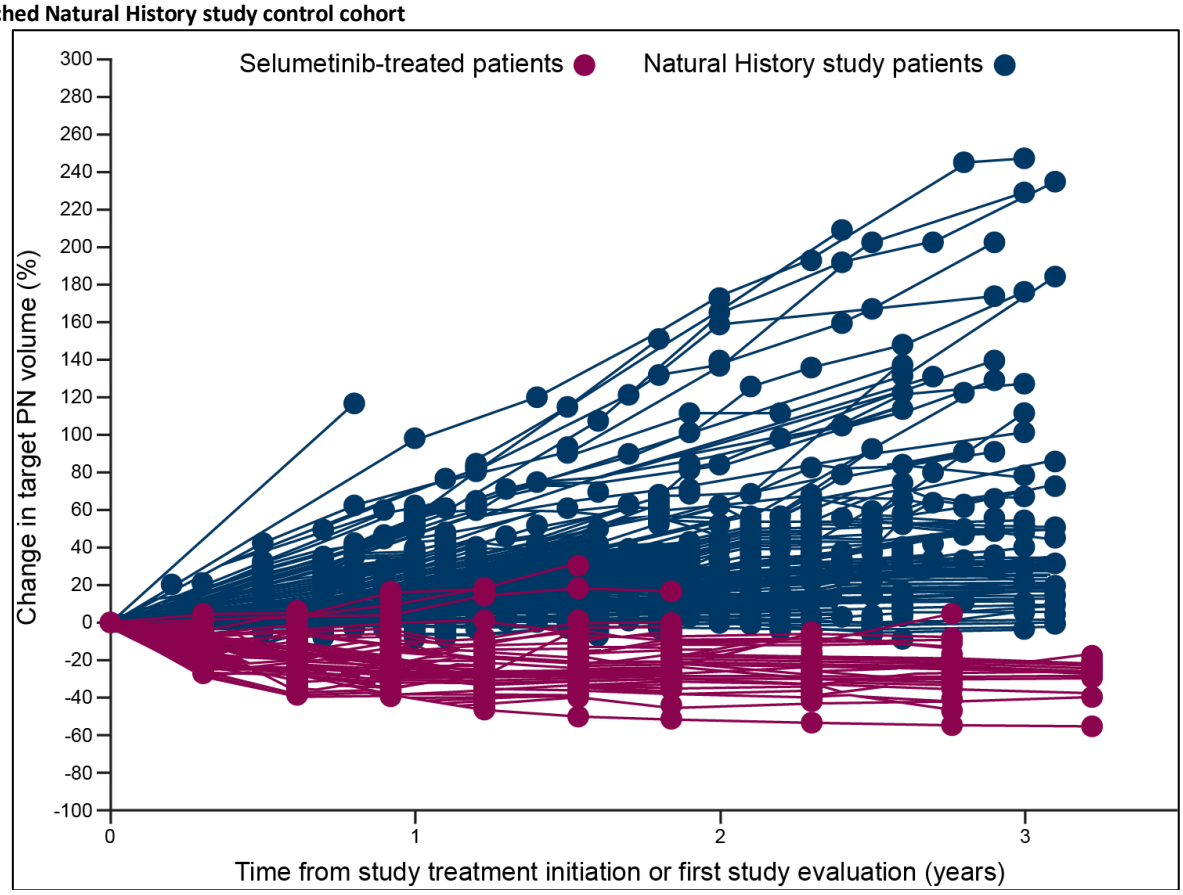
Selumetinib demonstrated clear efficacy in reversing or stabilising PN volume growth when compared with the NH study age-matched cohort, for the three-year follow-up period (Table 7 and Figure 6). No patients receiving selumetinib displayed a PN growth rate of ≥20% per year (range -27.0%–19.8% per year), 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 [42].

Table 7. Naïve comparison of SPRINT Phase 2 Stratum I to Natural History age-matched cohort for PN growth rate

Measure - PN growth rate	SPRINT Phase 2 Stratum I (N=50)	Natural History age-matched cohort (N=93)
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 – +1,429)

Source: Gross et al. 2020. [42]

Figure 6. Percentage change in target PN volume during selumetinib treatment in SPRINT Phase 2 Stratum I compared to an age-matched Natural History study control cohort



Source: Gross et al. 2020. [42]

7.1.4.2 Progression-free survival (PFS)

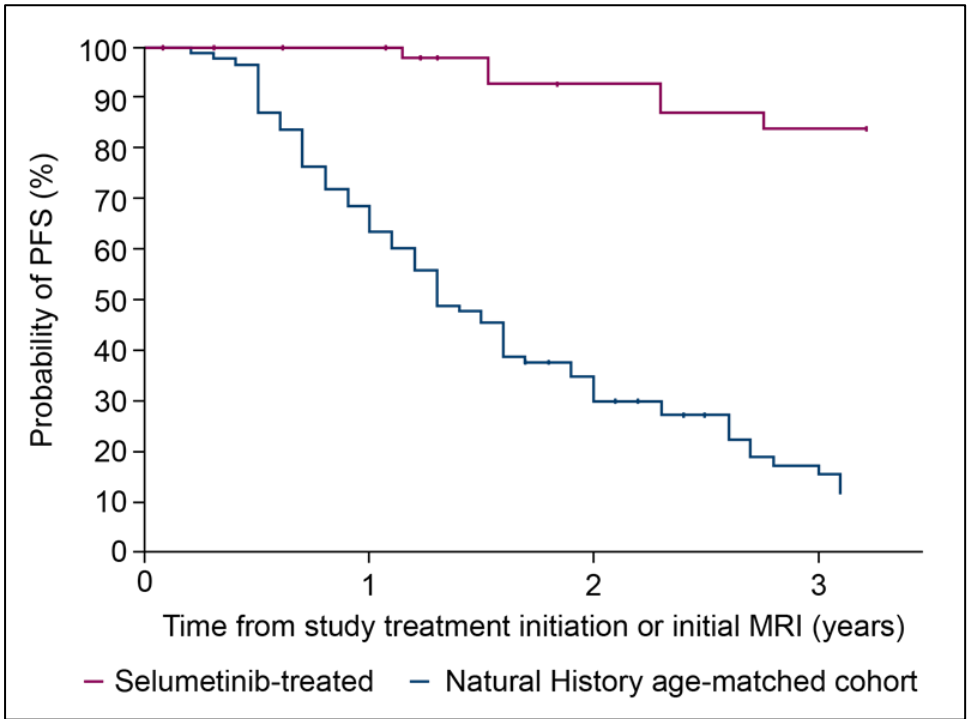
Median PFS was not reached in SPRINT Phase 2 Stratum I at DCO 29th March 2019 (Table 8). Based on the Kaplan-Meier estimates, there was a continued divergence in PFS between patients receiving selumetinib in SPRINT Phase 2 Stratum I and patients in the NH Study age-matched cohort, over the duration of the follow-up period (Figure 7). At three years, 84% of patients in SPRINT are estimated to be progression-free, compared with 15% in the Natural History age-matched cohort [42]. At the 27th of February 2021 DCO, five years since the start of treatment, median PFS in SPRINT Phase 2 Stratum I was still not reached [78]. Therefore, selumetinib offers significant benefits to patients, through prevention of PN volume growth and consequently prevention of disease progression.

Table 8. Naïve comparison of SPRINT Phase 2 Stratum I to Natural History age-matched cohort for PFS

Measure - PFS (over 3.2 years of follow-up)	SPRINT Phase 2 Stratum I (N=50)	Natural History age-matched cohort (N=93)
Median PFS, years (95% CI)	N/A[a]	1.3 (1.1–1.6)
Probability of PFS at 3 years, %	84	15

[a]The median PFS has not yet been reached, with only 12% of patients experiencing disease progression (6/50) Source: Gross et al. 2020. [42]

Figure 7. PFS during selumetinib treatment in SPRINT Phase II Stratum I compared to the age-matched Natural History study control cohort



Number of patients at risk	Year 0	Year 1	Year 2	Year 3
Natural History age-matched cohort	65	43	21	15
Selumetinib-treated	50	41	16	0

Source: Gross et al. 2020. [42]

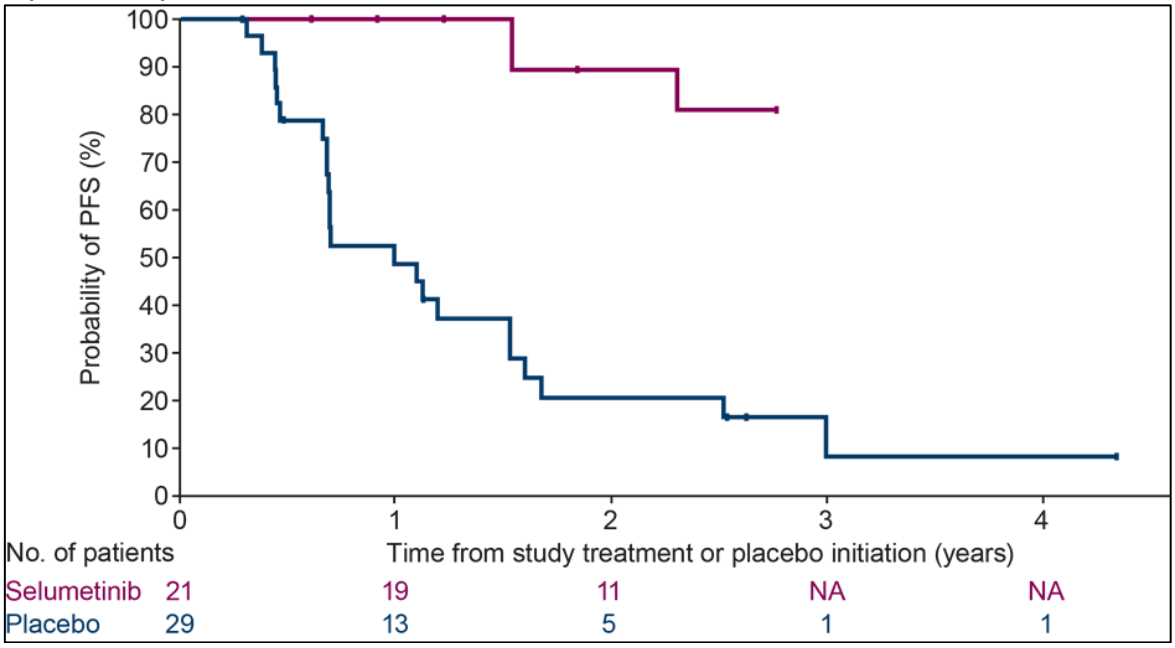
An additional naïve comparison was conducted to compare the results of the SPRINT Phase 2 Stratum I study and external control data from the placebo arm of the tipifarnib Phase 2 study 01-C-0222 [71, 77]. In the absence of data from Gross et al. 2020 (29th of March 2019 DCO) [42], data from the CSR (29th of June 2018 DCO) were used for this evaluation [71]. As only patients with progressive PN were enrolled in study 01-C-0222 [77], only patients from SPRINT Phase 2 Stratum I with progressive PN were used for the comparison [71].

Based on the 29th of June 2018 DCO, 21 of the patients included in SPRINT Phase 2 Stratum I had progressive PN in the 18 months prior to enrolment. 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 89% (95% CI 62.4–97.1) for the subgroup of patients with progressive PN at enrolment receiving selumetinib in SPRINT (Figure 8). Therefore, selumetinib is effective in preventing disease progression in symptomatic, inoperable PN which are actively growing [71]. These findings are consistent with the NH study comparisons presented above (Figure 7 and Table 8).

Moreover, Danish experts familiar with the clinical practice considered it reasonable that once a patient reaches adulthood (18 years of age), there will be no significant tumour volume growth [52]. The conclusion by Akshintala [39] also supports this, with a 0.07% annual growth rate in adults. Given the limited progression data from SPRINT, the model assumes a simple annual probability of progression based on PFS data reported by Gross et al. (2020)[42] (84%

at 3 years for patients receiving selumetinib). An updated propensity score method analysis that compared the risk of tumour progression between patients treated with selumetinib from the SPRINT trial compared with the NH external control arm accounted for tumour location, volume and status, the conclusion that the risk of tumour progression is significantly decreased with selumetinib was consistent with the initial age-matched and propensity score analyses.

Figure 8. Kaplan-Meier plot of PFS for selumetinib (patients with progressive PN from SPRINT Phase 2 Stratum I) versus placebo arm of tipifarnib Study 01-C-0222



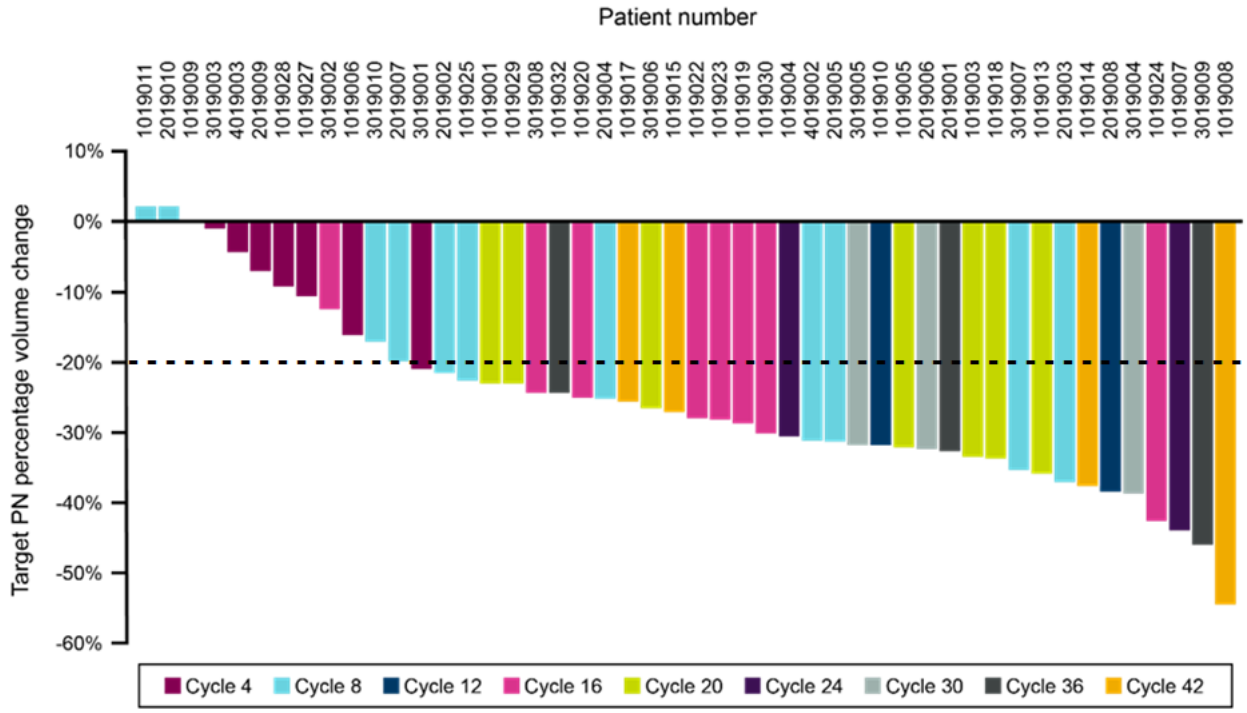
DCO for SPRINT data: 29th June 2018. Includes patients with progressive disease in the 18 months prior to enrolment in SPRINT Phase 2 Stratum 1. PFS was defined as the time from study treatment/placebo initiation until the pre-cycle/date of objective progression or death (by any cause in the absence of progression) for SPRINT Phase 2 Stratum 1/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.
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

7.1.4.3 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 contrasts with the unpredictable and uncontrolled growth experienced by patients enrolled on the NH study; a 77% increase in volume from baseline was observed in the age-matched NH study cohort [8], [42].

Most patients (45/50; 90%) treated with selumetinib in SPRINT Phase 2 Stratum I had a 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. A total of 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. 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 [42]. A waterfall plot showing the best volumetric response for each target PN, and the cycle during which this best response was achieved, is presented in Figure 9.

Figure 9. Best volumetric response from baseline in target PN volume in SPRINT Phase 2 Stratum I



The cut-off for partial response, a ≥20% reduction in PN volume, is indicated with the dotted line.
Source: Gross et al. 2020. [42]

BOR was evaluated again by the NCI for the 27th of February 2021 DCO and compared with the most recent response prior to the DCO. Median change in PN volume at best response remained at -27.2% (range -60.3 – 2.2). At this DCO, 50% of patients (25/50) had a confirmed response, 24% of patients (12/50) had stable disease and 22% of patients (11/50) were found to have developed progressive disease [78].

7.1.4.4 Duration of response

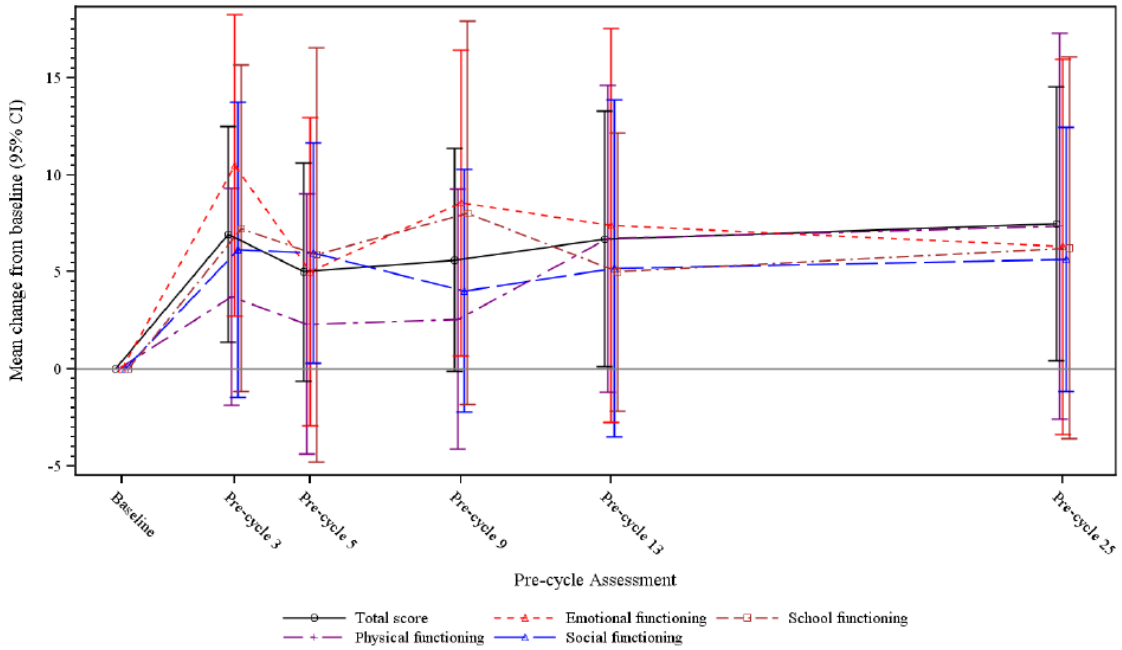
The median time to initial response in SPRINT Phase 2 Stratum I was 8 cycles (range 4–20), and the median time to best response was 16 cycles (range 4–36). Of the 35 patients who had confirmed PR to selumetinib, 28 (80%) had a durable response to selumetinib treatment, defined as a response lasting for more than one year. Median duration of response was not reached after three years of follow-up [42]. At the 27th of February 2021 DCO (5 years of follow-up) there was no change to the median time to best response and 28 patients demonstrated a durable response to selumetinib [78].

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 several years [42].

7.1.4.5 Health-related quality of life

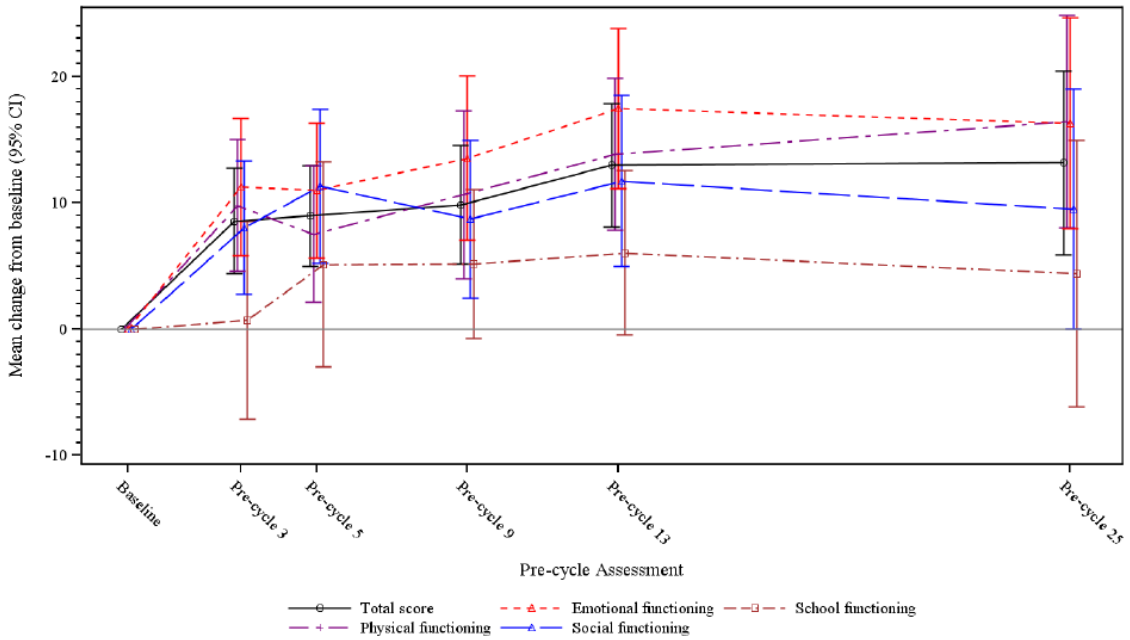
Overall, a trend of improvement in self- and parent-reported HRQoL scores was seen over each measurement cycle, based on mean change from baseline in both PedsQL total score and domain scores (Figure 10 and Figure 11) [71]. Improvements were maintained across all domain scores of the PedsQL.

Figure 10. Mean change from baseline in PedsQL self-reported scores



N=34. Children, ages 8 to 18 years of age at enrolment, completed self-report measures of the PedsQL.
Source: AstraZeneca Data on File (SPRINT CSR; DCO 29th June 2018) [71].

Figure 11. Mean change from baseline in PedsQL parent-reported scores



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.
Source: AstraZeneca Data on File (SPRINT CSR; DCO 29th June 2018) [71].

A mixed model repeated measures (MMRM) analysis of change from baseline in PedsQL total score was performed, as shown in Table 9. 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 a patient's HRQoL [71].

Table 9. Change from baseline PedsQL patient- and parent-reported outcomes total score (MMRM)

PedsQL total score	Selumetinib, n									
	Self-reported (n=34[b])					Parent-reported (n=50[c])				
	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	31	31	31	29	23	47	47	48	45	35
Adjusted mean	6.6	4.7	5.3	6.7	9.4	8.5	9.0	9.7	12.7	13.2
Standard error	1.8	2.1	2.2	2.6	3.0	1.7	1.8	2.0	1.9	2.7
95% CI	2.8, 10.3	0.3, 9.0	0.7, 9.8	1.3, 12.0	3.1, 15.8	5.1, 11.9	5.4, 12.5	5.7, 13.8	8.9, 16.6	7.8, 18.6
p-value[a]	0.001	0.036	0.024	0.016	0.006	<0.001	<0.001	<0.001	<0.001	<0.001

[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.
Source: AstraZeneca Data on File (SPRINT CSR; DCO 29th June 2018) [71].

Clinically meaningful thresholds (CMTs) of ≥10.33 and ≥11.90 were established for the analysis of the PedsQL self- and parent-reported scores respectively (estimated using anchor and distribution based approaches, and literature estimates from Varni et al. 2003 [79]). Impaired "global" HRQoL was defined as total or domain scores falling one standard deviation below the population sample mean [76, 79].

Based on self-reported PedsQL total scores [71]:

- 11/33 (33%) of patients had impaired "global" HRQoL at baseline.
- At pre-Cycle 13, 9/29 (31%) of patients had impaired "global" HRQoL, and 11/29 (38%) of patients showed a clinically meaningful improvement in global HRQoL above the CMT.
- At pre-cycle 25, only one patient (1/23; 4%) had impaired "global" HRQoL, and 7/23 (30%) of patients showed a clinically meaningful improvement in HRQoL above the CMT.

Based on parent-reported PedsQL total scores [71]:

- 28/50 (56%) patients had impaired "global" HRQoL at baseline.
- At pre-Cycle 13, 16/45 (36%) patients with parent-reported scores had impaired "global" HRQoL, and 24/45 (53%) of patients showed an improvement in HRQoL based on the CMT.
- At pre-cycle 25, 11 patients (11/35; 31%) had impaired "global" HRQoL and 19/35 (54%) patients showed a clinically meaningful improvement in HRQoL above the CMT.

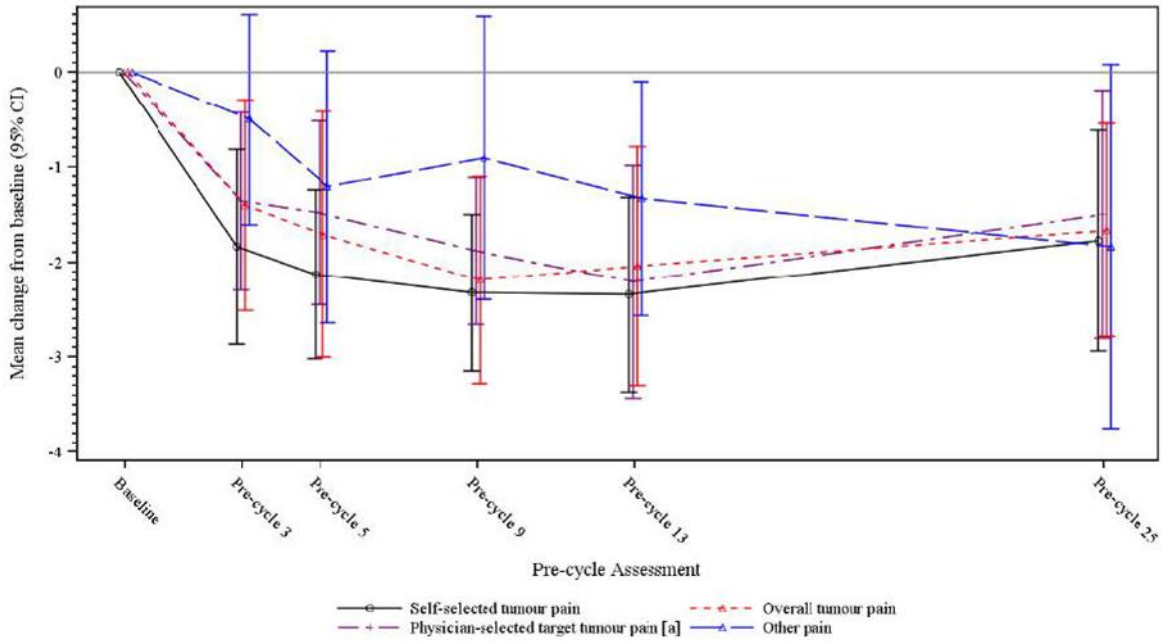
The parent-reported scores showed a greater percentage of patients with impaired "global" HRQoL at baseline, and a greater clinically meaningful improvement in patient HRQoL. Nonetheless, a substantial proportion of both patients and parents reported meaningful improvements in HRQoL with selumetinib treatment [71]. This indicates a sustained benefit of treatment with selumetinib on patients' HRQoL as perceived by patients as well as their parents [71].

7.1.4.6 PN-associated pain

The NRS-11 was used to assess pain intensity. Patients aged 8 to 18 years at enrolment completed self-report measures of NRS-11.

Improvement in pain intensity for self-selected tumour pain, target tumour pain, overall tumour pain and other pain, was seen as early as pre-Cycle 3. This improvement was maintained through pre-Cycle 25. Mean change from baseline in pain intensity scores over time is presented in Figure 12.

Figure 12. Mean change from baseline of NRS-11 pain intensity scores



[a]24 patients completed NRS-11 assessments for physician-selected target tumour pain at baseline and at the pre-Cycle 13 visit. 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.
Source: AstraZeneca Data on File (SPRINT CSR; DCO 29th June 2018) [71].

Physician-selected target tumour pain is considered the most clinically relevant item, as it assessed the pain intensity caused by the target PN. In total, 24 patients completed NRS-11 assessments for physician-selected target tumour pain at baseline and at the pre-Cycle 13 visit [71]:

- The median score for target tumour pain intensity at baseline was 2.5 (range 0–10), compared to 0 at pre-Cycle 13 (range 0–7), showing a clear reduction in pain intensity.
- 12/24 patients (50%) showed improvement of ≥2 points, considered clinically meaningful using the established CMT of 2 points based on published literature[80-83].
- 10 of the 12 patients who showed no change in tumour pain intensity had a pain score of 0 or 1 at baseline and therefore could not improve their score by two points or more.

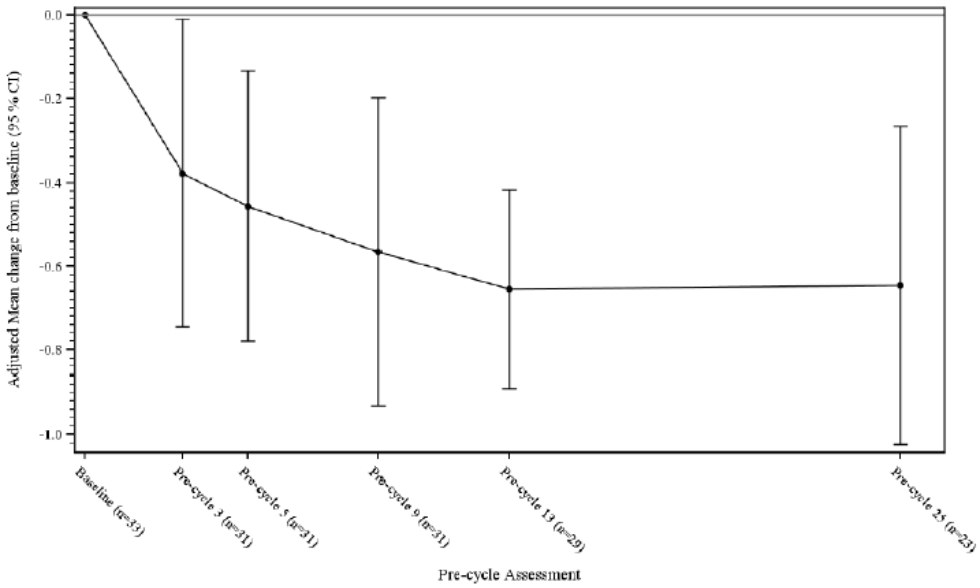
- No patients showed deterioration at pre-Cycle 13.

A decrease from baseline in target tumour pain intensity scores was also seen at each measurement cycle based on MMRM analysis. At pre-Cycle 13, the adjusted mean change from baseline in physician-selected target tumour pain was -2.07 (95% CI -2.84 to -1.31), considered clinically meaningful. This meaningful change was maintained through to pre-Cycle 25 [71].

Associations between post-baseline longitudinal changes in NRS-11 and changes in PN volumes were also assessed. MMRM analysis models were fitted with absolute changes in NRS-11 and the percentage change in tumour volume as a covariate. After adjusting for age, number of morbidities, and the baseline value of the outcome, there was evidence of a meaningful correlation between percentage change from baseline in target PN volume and change in NRS-11 score ($p<0.001$) [71]. When results from the NRS-11 were compared to data collected on pain medication use, it was found that 14 patients 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 two to four months of treatment, with the median time to pain palliation being reached by pre-Cycle 3 [71].

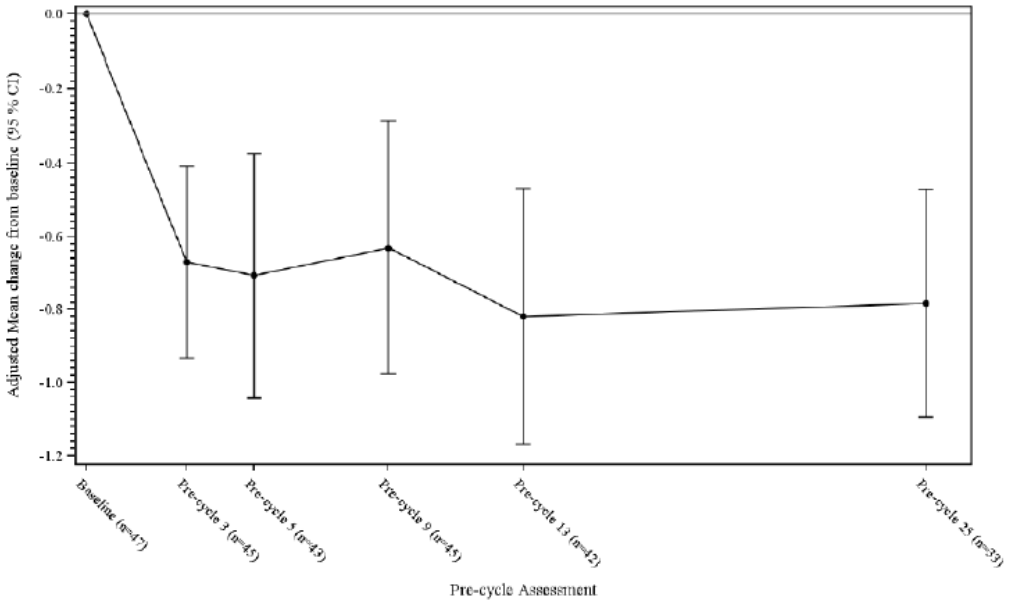
The pain interference index (PII) was used to assess pain interference with daily functioning. Both patients and parents reported a decrease in pain interference from baseline at pre-Cycle 13 based on MMRM analysis of PII scores. Improvement from baseline in self-reported and parent-reported PII scores was consistently observed at each measurement cycle (Figure 13 and Figure 14) [71].

Figure 13. Mean change from baseline in PII self-reported pain interference total score (MMRM)



Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the PII (n=34).
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

Figure 14. Mean change from baseline in PII parent-reported pain interference total score (MMRM)



Parents or legal guardians of patients aged 5 to 18 years at enrolment expected to complete the parent proxy PII (n=48).
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

A CMT of 0.75 was used for analysis of self-reported PII (CMT estimated using anchor and distribution-based approaches) [71]:

- For the 29 patients who completed self-reported PII assessments at baseline and at pre-Cycle 13, a reduction in the median score for target tumour pain interference was seen (0.67 at baseline to 0 at pre-Cycle 13).
- 10/29 (35%) showed a clinically meaningful (≥0.75) improvement.
- One patient showed deterioration at pre-Cycle 13.

These results were replicated for the parent-reported PII assessments. A CMT of 1.78 was used for analysis of parent-reported PII (estimated using anchor and distribution-based approaches) [71]:

- For the 42 patients who had parent-reported PII assessments at baseline and at pre-Cycle 13, a reduction in the median score for target tumour pain interference was seen (1.50 at baseline to 0.17 at pre-Cycle 13).
- 14/42 (33%) showed a clinically meaningful (≥1.78) improvement.
- Three patients showed deterioration at pre-Cycle 13.

Analyses of NRS-11 and PII results have also been performed for the 27th of February 2021 DCO. At this DCO, 19 patients completed NRS-11 while 18 patients and 24 parents completed the PII. A statistically significant improvement in pain interference was maintained from pre-Cycle 13. These results demonstrate the persistence of the improvement in PN-associated pain with selumetinib treatment over a period of approximately 4 years [78].

Results of the NRS-11 and PII demonstrate the capacity of selumetinib to have a positive, clinically meaningful impact on PN-associated pain, with decreases in both the pain intensity and pain interference in daily life experienced by

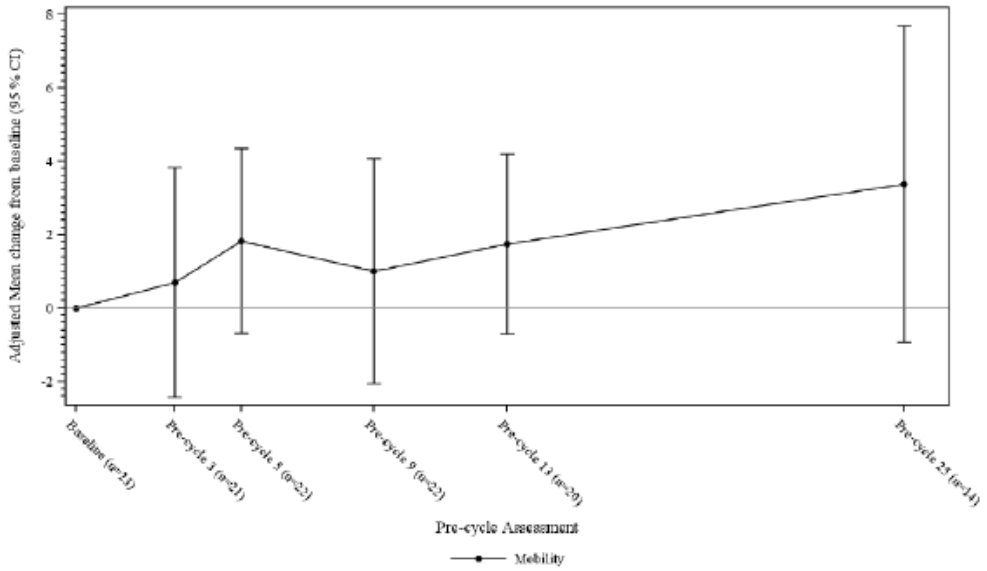
patients. PN-associated pain decreased over one year and stabilized over long-term treatment. Additionally, patients in SPRINT Phase 2 Stratum I did not require increases in pain medications over time, in contrast to patients enrolled on the NH study. This again demonstrates the positive impact of selumetinib.

7.1.4.7 Motor function

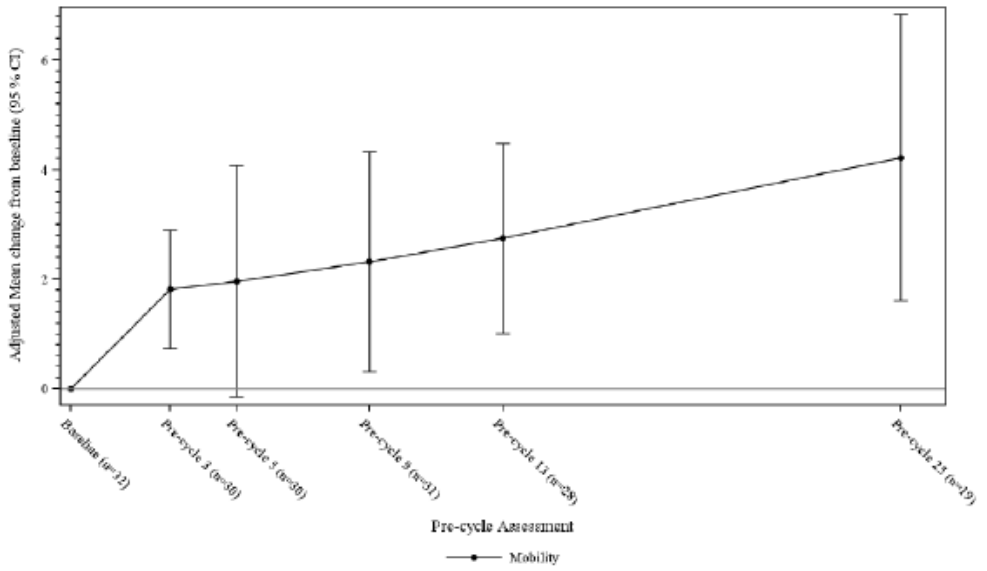
Physical functioning and physical activity were assessed through the PROMIS mobility and upper extremity scales. There was a trend towards improvement in mobility at each timepoint (Figure 15), and a trend towards improvement in upper extremity physical function at pre-Cycle 25 (Figure 16), as reported by both parents and patients [71].

Figure 15. Adjusted mean change from baseline of PROMIS® self- and parent-reported scores, mobility (MMRM)

A: Self-report

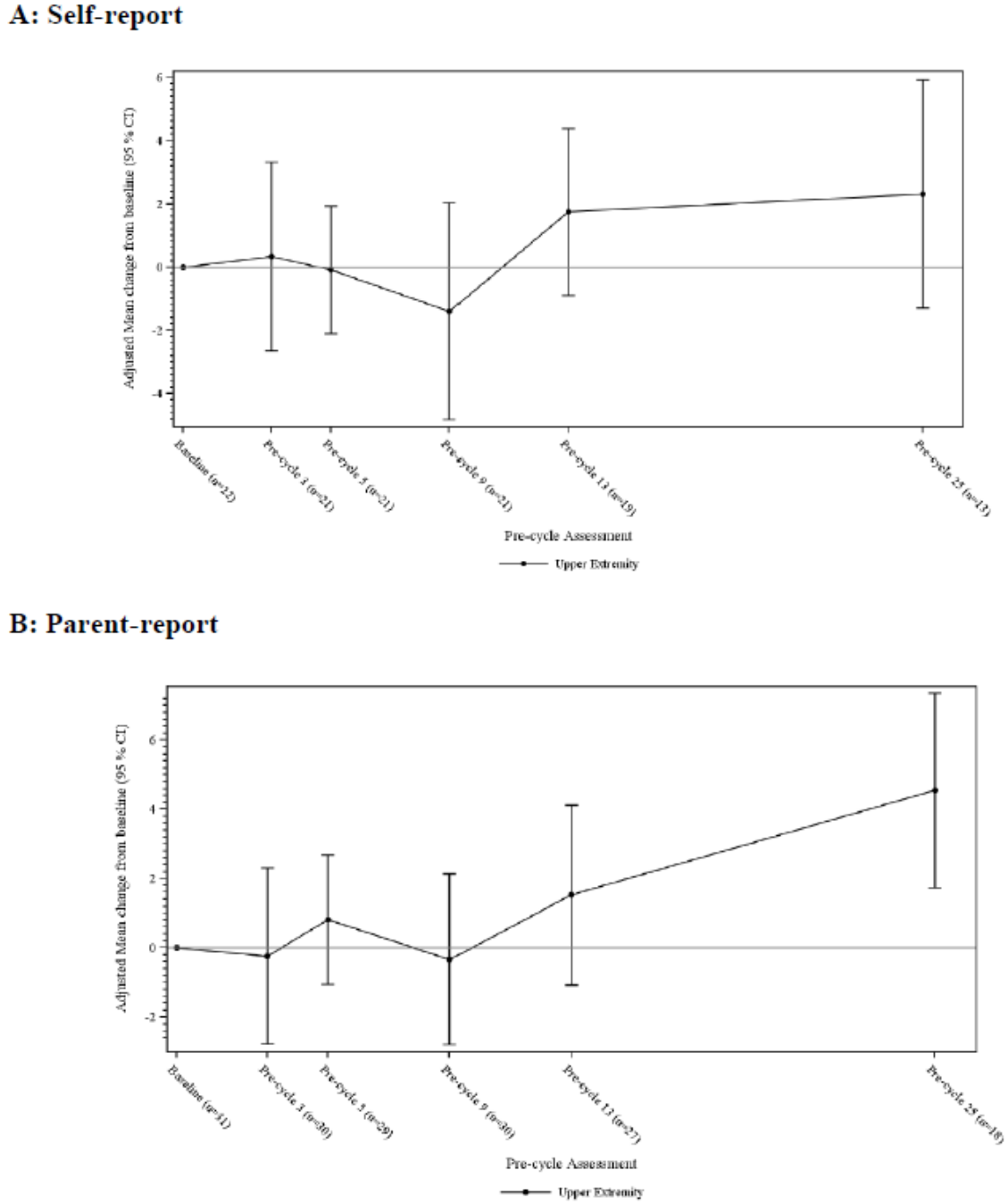


B: Parent-report



A: Self-reported, n=24. B: Parent reported, n=33
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

Figure 16. Adjusted mean change from baseline of PROMIS® self- and parent-reported scores, upper extremity (MMRM)



A: Self-reported, n=24. B: Parent reported, n=33.
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

Raw scores for mobility and upper extremity were converted into T-scores, which are based on reference data from the US general population (where mean=50 and SD=10.0). Between baseline and pre-Cycle 13, the mean T-scores showed clinically meaningful improvements in 6/20 (30%) of patients for the patient-reported mobility and 5/19 (26%) of the patients for the upper extremity scores. The mean T-scores also showed clinically meaningful improvements in 9/28 (32%) of patients for the parent-reported mobility and 4/27 (15%) of patients for the upper extremity scores [71].

Manual muscle testing (MMT) demonstrated improvement in the average strength of the muscles in the same body quadrant as the target PN over time. At baseline, the median muscle strength score in the affected body quadrant was 4.6. When scores were adjusted for age, there was an increase from mean baseline strength score observed at each timepoint for the muscle groups in the PN-related body quadrant. In the MMRM analysis of the of strength MMT, there was an improvement in strength at pre-Cycle 13 and pre-Cycle 25 compared to baseline, regardless of the location of the patient's target PN. Improvement in strength was observed at pre-Cycles 9 and 13 for patients with unilateral upper PN and at pre-Cycle 13 for patients with unilateral lower PN [71].

In an MMRM analysis of patients with a target PN in any body quadrant, improvement in range of motion was seen, from pre-Cycle 5 through pre-Cycle 25. There was also a trend towards improvement in range of motion over time for patients with unilateral lower PN [71].

Overall, these results demonstrate improvements in mobility, upper extremity scores, range of motion and strength, particularly 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 NH study where growth of PN over time was observed to lead to increasing severity of motor dysfunction [8].

7.1.4.8 Airway function

Sixteen patients had airway dysfunction at baseline, however five patients with tracheostomy were excluded from the functional evaluations [71]:

- FEV1: There was a trend for improvement in FEV1 from baseline to pre-Cycle 13. At pre-Cycle 13, 7/11 (63%) patients showed improvement. This trend in improvement was maintained through to pre-Cycle 25. 4/11 patients (36%) showed no change, and no patients showed deterioration.
- R20: Resistance trended towards worsening at pre-Cycles 5 and 9 but improved by pre-Cycle 13 (mean change from baseline -0.079).
- AHI: At baseline, no patient had an AHI of >5 events per hour. Therefore, no patient met the REiNS criteria (>5 events/hour) for inclusion in sleep studies.

The observed effect on FEV1 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.

7.1.4.9 Bowel and bladder function

Due to insufficient responses at baseline (n=2), it was not possible to assess self-reported outcomes of bowel and bladder function using the dysfunctional voiding questionnaire (DVQ). A trend for improvement at pre-Cycle 13 compared to baseline was reported by parents for their children (n=8). However, the confidence intervals were wide [71].

7.1.4.10 Visual function

Baseline and pre-Cycle 13 assessments for visual acuity were reported for four patients. Mean visual acuity trended towards slight deterioration for the affected eye by pre-Cycle 13. However, these changes may be impacted by the small number of patients and variability due to patient age. Mean visual acuity remained stable over time for the non-affected eye [71].

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, one (14%) patient showed improvement, four (57%) patients showed no change and two (29%) patients showed deterioration in exophthalmometry [71]. 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 [71].

7.1.4.11 Disfigurement

Improvements in disfigurement from baseline in PN in a range of locations, including the head and neck, trunk and extremities of the body were seen with selumetinib treatment [71]. With disfiguring facial PN in particular having been shown to have a negative impact on patients' social/physical functioning and self-esteem [65, 84], it can be expected that this effect of treatment with selumetinib would result in a wide-reaching benefit on patients' lives.

7.1.5 Secondary outcome: Global impression of change (GIC)

In SPRINT Phase 2 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 [71].

For both self-reported and parent-reported GIC, there were improvements in tumour pain, overall pain, and tumour-related morbidity at each time point through pre-Cycle 25 (summarised in Table 10, Table 11 and Table 12 respectively). Worsening of pain was rarely reported [71]. This indicates an overall positive trend in the perception of PN-related morbidity over time as a result of treatment with selumetinib.

Table 10. Distribution of GIC self- and parent-reported tumour pain over time

Response category	Selumetinib (n)					
	Self-reported (n=34)			Parent-reported (n=48)		
	Pre-cycle 3	Pre-cycle 13	Pre-cycle 25	Pre-cycle 3	Pre-cycle 13	Pre-cycle 25
Total responses	26	29	23	38	43	34
Very much improved	7 (27)	10 (35)	11 (48)	2 (5)	14 (33)	11 (32)
Much improved	5 (19)	5 (17)	5 (22)	7 (18)	11 (26)	9 (27)
Minimally improved	6 (23)	7 (24)	1 (4)	11 (29)	3 (7)	4 (12)
No change	7 (27)	6 (21)	6 (26)	16 (42)	15 (35)	10 (29)
Minimally worse	1 (4)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)
Much worse	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)

Very much worse	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Patients aged 8 to 18 years at enrolment were expected to complete self-report measures of the GIC. Percentages were based on the number of patients with a non-missing score at each analysis visit.
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

Table 11. Distribution of GIC patient- and parent-reported overall pain over time

Response category	Selumetinib (n)					
	Self-reported (n=34)			Parent-reported (n=48)		
	Pre-cycle 3	Pre-cycle 13	Pre-cycle 25	Pre-cycle 3	Pre-cycle 13	Pre-cycle 25
Total responses	30	29	23	44	43	34
Very much improved	6 (20)	6 (21)	6 (26)	2 (5)	10 (23)	10 (29)
Much improved	3 (10)	6 (21)	3 (13)	8 (18)	12 (28)	8 (24)
Minimally improved	6 (20)	5 (17)	6 (26)	12 (27)	6 (14)	5 (15)
No change	12 (40)	12 (41)	8 (35)	21 (48)	13 (30)	10 (29)
Minimally worse	3 (10)	0 (0)	0 (0)	0 (0)	1 (2)	1 (3)
Much worse	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
Very much worse	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Patients aged 8 to 18 years at enrolment were expected to complete self-report measures of the GIC. Percentages were based on the number of patients with a non-missing score at each analysis visit.
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

Table 12. Distribution of GIC patient- and parent-reported tumour-related morbidity over time

Response category	Selumetinib (n)					
	Self-reported (n=34)			Parent-reported (n=48)		
	Pre-cycle 3	Pre-cycle 13	Pre-cycle 25	Pre-cycle 3	Pre-cycle 13	Pre-cycle 25
Total responses	23	29	23	34	43	34
Very much improved	4 (17)	10 (35)	8 (35)	0 (0)	15 (35)	13 (38)
Much improved	5 (22)	7 (24)	8 (35)	6 (18)	16 (37)	11 (32)
Minimally improved	7 (30)	4 (14)	3 (13)	12 (35)	6 (14)	6 (18)
No change	6 (26)	7 (24)	4 (17)	13 (38)	5 (12)	3 (9)
Minimally worse	1 (4)	1 (3)	0 (0)	3 (9)	1 (2)	1 (3)
Much worse	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Very much worse	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Patients aged 8 to 18 years at enrolment were expected to complete self-report measures of the GIC. Percentages were based on the number of patients with a non-missing score at each analysis visit.
Source: AstraZeneca Data on File (SRINT CSR; DCO 29th June 2018) [71].

7.1.6 Safety

7.1.6.1 Exposure

At DCO (29th March 2019, 90DSU), 32 (64%) patients were receiving selumetinib treatment. The difference between the median total and median actual treatment duration was small (83.5 days), 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 13 [85]. Furthermore, at a more recent DCO dated 27th February 2021, 23 (46%) subjects remained on treatment, with a median treatment duration of 52.5 cycles (1,470 days, or approximately 4 years) [78].

Table 13. Exposure to selumetinib

AEs	Selumetinib (N=50)
Total treatment duration (days)[a]	
Mean (SD)	892.7 (356.6)
Median (min–max)	1027.5 (28.0–1326.0)
Total treatment years	122.2
Total treatment duration (months)[b]	
<12 months, n (%)	6 (12)
≥12 to ≤24 months, n (%)	9 (18)
>24 to ≤36 months, n (%)	18 (36)
>36 to ≤48 months, n (%)	17 (34)
>48 months, n (%)	0 (0)
Actual treatment duration (days)[c]	
Mean (SD)	825.3 (339.7)
Median (min–max)	944.0 (26.0–1290.0)
Total treatment years	113.0

[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.
Source: AstraZeneca Data on File (90 day safety update) [85].

7.1.6.2 Adverse events

A summary of AEs in SPRINT Phase 2 Stratum I is presented in Table 14 [85]. Although most patients in the trial reported AEs (98%), they were mostly non-serious. Only 24% of patients experienced SAEs and 12% of patients experienced treatment-emergent SAEs. There were no deaths during the study. These AEs could generally be managed using dose interruptions, symptomatic or supportive care, and subsequently resolved. 84% of patients experienced dose interruptions due to AEs and only 12% of patients discontinued due to AEs. Consistent with previous safety assessments for selumetinib, no irreversible or cumulative toxic effects were noted [85]. At a more recent DCO dated 27th February 2021, most subjects (n=49) had ≥1 AE at least possibly related to treatment (97% grade ≤ 2) [78]. To conclude, the safety and tolerability profile of selumetinib is suitable for long-term treatment since AEs can usually be managed without the need for discontinuation.

Table 14. Summary of adverse events

AEs	Selumetinib (N=50)

All grade AEs, n (%)	49 (98)
Grade ≥3 AEs, n (%)	31 (62)
Treatment-emergent grade ≥3 AEs, n (%)	20 (40)
SAEs, n (%)	12 (24)
Treatment-emergent SAEs, n (%)	6 (12)
Deaths, n (%)	0 (0)
Dose interruptions due to AEs, n (%)	42 (84)
Dose reductions due to AEs, n (%)	13 (26)
Discontinuations due to AEs, n (%)	6 (12)

Source: AstraZeneca Data on File (90 day safety update) [85].

7.1.6.2.1 Common AEs

A summary of the most common AEs (experienced by ≥50% of patients) experienced in SPRINT Phase 2 Stratum I is presented in Table 15. The two most common AEs experienced were vomiting (82% of patients) and increased blood creatine phosphokinase (76% of patients) [85]. At DCO 27th February 2021, most common AEs were gastrointestinal symptoms, asymptomatic CPK increase, paronychia, and acneiform rash [78].

Table 15. Common AEs (≥50%)

AEs, Preferred term (PT)	All grade AEs, selumetinib (N=50), n (%)
Vomiting	42 (84)
Blood creatine phosphatase increased	38 (76)
Diarrhoea	37 (74)
Nausea	35 (70)
Dry skin	32 (64)
Pyrexia	30 (60)
Fatigue	28 (56)
Dermatitis acneiform	26 (52)
Hypoalbuminemia	26 (52)

Headache	25 (50)
Oropharyngeal pain	25 (50)
Stomatitis	25 (50)

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.
Source: AstraZeneca Data on File (90 day safety update) [85].

7.1.6.2.2 Grade ≥3 AEs

Grade ≥3 AEs were reported in 62% (31/50) of selumetinib-treated patients (Table 16) [85]. AEs of Grade ≥3 were most commonly reported in the system organ class (SOC) of gastrointestinal disorders. No discernible patterns were observed for Grade ≥3 AEs, with the events being dispersed across multiple system organ classes. By preferred term (PT), the most commonly reported AEs of Grade ≥3 were diarrhoea (16%), hypoxia (8%), pyrexia (8%), vomiting and weight increased (8%). At DCO 27th February 2021, only three Grade 4 AEs possibly related to selumetinib had been observed: creatine phosphokinase increased, hyperuricemia and skin ulceration [78].

Table 16. AEs for CTCAE Grade ≥3

SOC/MedDRA preferred term	Selumetinib (N=50), n (%)[a]
Patients with AE CTCAE Grade ≥3, n (%)	31 (62)
Gastrointestinal disorders	13 (26)
Diarrhoea	8 (16)
Vomiting	4 (8)
Dental caries	2 (4)
Nausea	2 (4)
Investigations	11 (22)
Weight increased	4 (8)
Blood creatine phosphokinase increased	3 (6)
Alanine aminotransferase increased	2 (4)
Lipase increased	2 (4)
Infections and infestations	9 (18)
Paronychia	3 (6)

Skin and subcutaneous tissue disorder	6 (12)
Dermatitis acneiform	3 (6)
Eczema	2 (4)
General disorders and administration site conditions	4 (8)
Pyrexia	4 (8)
Reparatory, thoracic, and mediastinal disorders	4 (8)
Hypoxia	4 (8)
Nervous system disorders	3 (6)
Syncope	2 (4)
Blood and lymphatic system disorders	2 (4)
Anaemia	2 (4)

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. Terms in bolds are used to categorize such AEs according to the MeDRA preferred term list. Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.
Source: AstraZeneca Data on File (90 day safety update) [85].

7.1.6.3 Dose interruptions

Whilst dose interruptions occurred in all selumetinib patients, single missed doses were counted as dose interruptions, contributing to the relatively high number of interruptions recorded [85].

The most common reasons for dose interruptions were 'other' (45 [90%] patients, including logistical issues such as dose not documented, travel issues and surgery) and patient compliance (42 [84%] patients) [85].

Dose interruptions of selumetinib due to AEs occurred in 41 (82%) patients [85]:

- The most common AEs (reported in >5 patients) that result in treatment interruption were vomiting (15 patients), nausea (9 patients), paronychia (8 patients), influenza-like illness (8 patients) and diarrhoea (6 patients), the majority of which are ADRs for selumetinib.
- Most events resulting in dose interruptions were related to selumetinib treatment.

At DCO 27th February 2021, 16 patients (33%) had at least one dose reduction, with five patients having two dose reductions due to toxicity. Of the 11 patients with progressive disease, eight had a dose reduction prior to progression [78].

7.1.6.4 Dose reductions

In total, 13 (26%) patients had dose reductions due to AEs [85]:

- All of these events resolved and were managed with symptomatic or supportive treatment where necessary.
- Most AEs that were causally attributed to selumetinib and led to dose reduction were Grade ≥3.
- The selumetinib ADRs which led to dose reductions included paronychia (4 [8%] patients), increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatine phosphokinase, diarrhoea and rash maculo-papular.

At DCO 27th February 2021, 16 patients (33%) had at least one dose reduction, with five patients having two dose reductions due to toxicity. Of the 11 patients with progressive disease, eight had a dose reduction prior to progression [78].

7.1.6.5 Discontinuations

Discontinuation of selumetinib due to AEs occurred in 6 (12%) patients [85]:

- All but one AE resolved after selumetinib was stopped. One AE of increased weight was still ongoing at DCO (29th Mar 2019, 90DSU).
- The most common system organ class AEs leading to permanent discontinuations was “investigations”.
- Most AEs leading to discontinuation (in 5/6 patients, 83%) were considered treatment-emergent, expect for creatine increase and MPNST.
- The most frequently observed AEs (in >40% of patients), including acneiform rashes and gastrointestinal events, did not generally lead to discontinuation of selumetinib.

Overall, results of SPRINT Phase 2 Stratum I indicate that selumetinib has a generally predictable and manageable safety profile in paediatric patients with symptomatic, inoperable NF1 PN and would be suitable for long-term treatment [85]. Moreover, at DCO 27th February 2021, no more patients discontinued selumetinib due to AEs [78].

7.1.7 Ongoing trial

The SPRINT (NCT01362803) Phase 2 Stratum I and Stratum II trials are still on-going with estimated completion date on January 1st, 2030. These open label, single-arm trials study the effect of selumetinib in patients aged 2–18 with NF1 and symptomatic, inoperable PN (Stratum I) or inoperable PN which have the potential to cause significant morbidity (Stratum II). Additionally, there is another ongoing phase 2, open label, single-arm trial (NCT02407405), which studies the effect of selumetinib in patients aged ≥18 with inoperable PN which are symptomatic or progressive. The estimated completion date of this study is the 1st of January 2025.

7.1.8 Comparative analyses of efficacy and safety

A propensity score analysis was performed for the comparison of PFS between selumetinib-treated patients from SPRINT Phase 2 Stratum I vs patients treated with established clinical management only from the NH study. For further details, see Appendix F – External control: Natural History study propensity score matched analysis

8. Health economic analysis

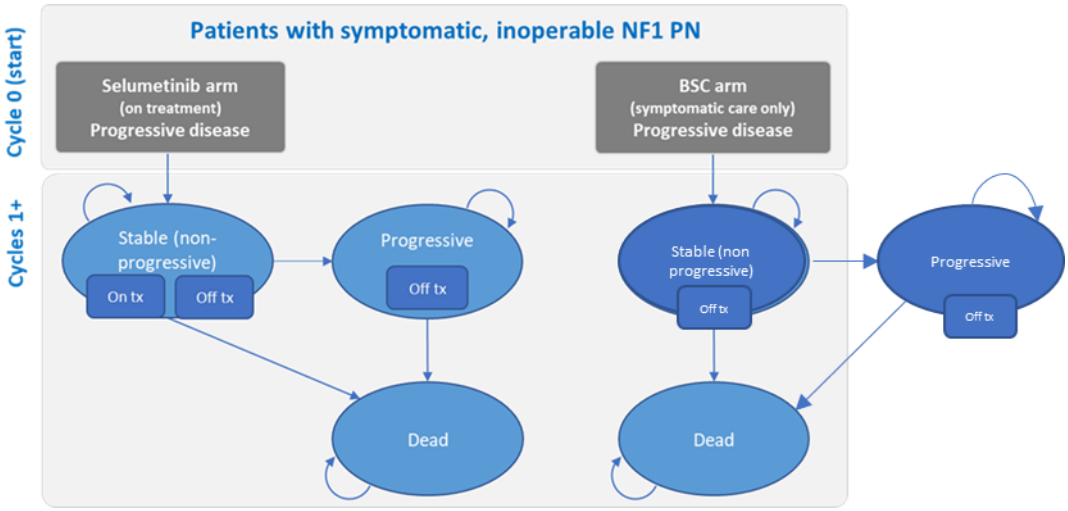
A health economics analysis was performed to investigate if selumetinib, on top of best supportive care (BSC) constitutes a cost-effective alternative to BSC alone in the treatment of paediatric patients with NF1 and symptomatic inoperable PN in Denmark.

8.1 Model

A simplified area under the curve (AUC) approach was deemed the most appropriate structure for estimating the cost-effectiveness of selumetinib compared with current BSC. This approach reduces the number of assumptions that would be required by alternative model structures due to the progressive natural history of NF1 PN, the disease heterogeneity, and the limited data availability.

In the model, health states are simplified into "non-progressed", "progressed" or "deceased". The model structure (see Figure 17) can be proxied as a four-state structure for the modelling of both the selumetinib and BSC arm, with some adjustments in the non-progressed state of the BSC arm to reflect the data and the development of the disease. Progression and duration of treatment are modelled independently. Progression is 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.

Figure 17. Model structure



The states in the model are as follows:

- Selumetinib:
  - On-selumetinib treatment, non-progressed
  - Off-selumetinib treatment, non-progressed
  - Off-selumetinib treatment, progressed
  - Dead
- Best supportive care:
  - Off-selumetinib treatment, non-progressed
  - Off-selumetinib treatment, progressed
  - Dead

In the BSC arm, patients enter the model with stable or non-progressed disease, and they could either maintain a progression-free state (PFS) or progress and experience PN growth. Once the patients transition to a progressed state, they remain in this health state until death. For the BSC PFS arm, standard parametric functions were fitted to the age-matched NH cohort following the goodness-of-fit criterium. This approach allows for more flexibility in the model, but presents some limitations and it is not entirely consistent with the available evidence. For instance, in the Gross et al. 2018 analysis of the NH study, no patients aged ≤18 years experienced a reduction in tumour volume from baseline. Across the study, a median growth rate of 15.9% per year was observed (lower quartile 10.1%, upper quartile 28.0%)[8]. While the PN growth rate experienced by individual patients varies, with some growing rapidly and others more slowly, the trend was for growth over of time. Therefore, patients treated with BSC experience persistent PN growth, even if this growth rate does not meet the formal definition of 'progressive disease' as used in the SPRINT Phase 2 Stratum 1 study (a ≥20% increase in PN volume) [8, 86], and subsequently in the cost-effectiveness analysis. In total, eight PN in the Gross *et al*. 2018 study of the NH study had a <20% relative volume difference between baseline and maximum assessment (volumetric assessment at which the PN was at its maximum volume). However, median growth in these eight PN was 14.2% (5.7% per year), demonstrating that despite being classified as 'stable', these PN were still undergoing growth [86]. Hence, the model is adjusted to take into account the development of PN for the BSC PFS state with respect to utility, to better reflect the two different experiences of PFS for the different treatments in the framework of the limited availability of data.

In the selumetinib arm, all patients enter the model on treatment and remain so until treatment discontinuation. Discontinuation is modelled via parametric models fit to patient-level data of time-to-discontinuation (TTD) from the SPRINT trial following the principles of partitioned survival modelling. Patients receiving selumetinib experience disease stabilisation within the first year of treatment and remain in the PFS until disease progression. PFS is modelled by a simple annual probability of progression based on PFS data from SPRINT in the base case. It is assumed that if patients have progressed, they are no longer on treatment.

The proportion of patients in each health state is recorded over time to plot a curve. The AUC for each health state is multiplied by health-state-specific costs, and by utility scores to derive the quality-adjusted life years (QALYs). The utility benefits accrued in these health states are dependent on whether a patient is progressed or non-progressed (and adjusted for age-related disutilities), and the costs accrued in these health states are dependent on whether a patient is on- or off-selumetinib treatment. The time horizon applied for the analysis is of 100 years, deemed to be sufficient to capture the benefits and the cost associated with the treatment. The cycle length used is of 1 year, and the model allow half cycle corrections. Discount rates used in the model for costs and benefits are in line with those listed in the Danish guideline [87] and are reported in Table 17.

Table 17. Discounts values used in the model

Years	Years 0-35	Years 36-70	Years > 70
Discount costs	3.5%	2.5%	1.5%
Discount benefits	3.5%	2.5%	1.5%

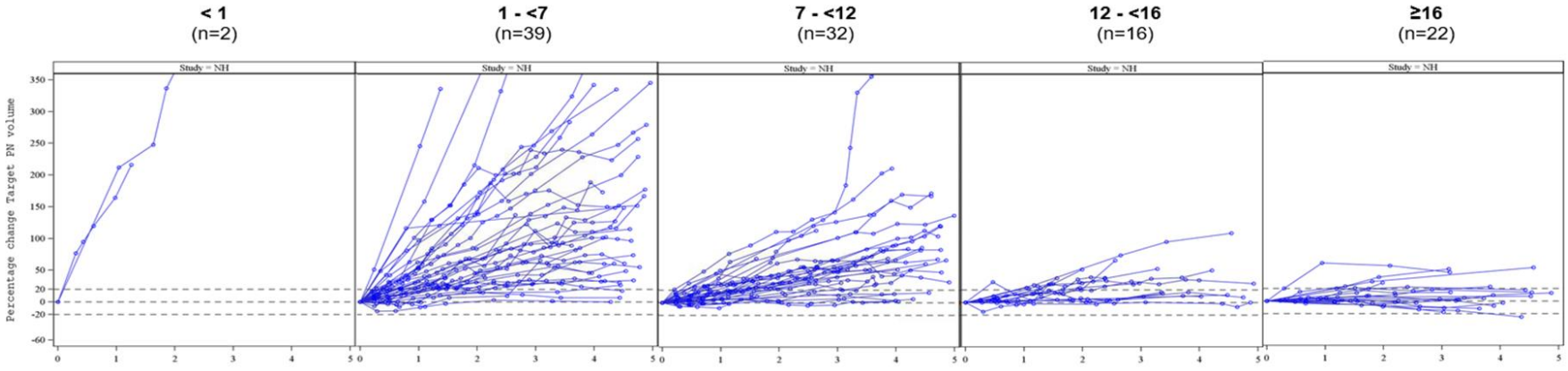
The utility values associated with progressed BSC (untreated patient) and selumetinib (treated patient) are assumed to be proxies for progressed and non-progressed health states, respectively, with the exception of the BSC PFS utility which is calculated as a midpoint between the two states. This solution was adapted to represent the fact that despite the lack of progression as defined by the trial criteria (a ≥20% increase), all the patients in the BSC arm were still suffering from PN growth. In the base case analysis, selumetinib patients start with the utility of an untreated patient and, if the patient

is being treated, this increases to the utility value of a treated patient over one year. BSC patients on the other hand start with BSC PFS utility, and either progress or maintain it in the following cycles. This solution was adopted to implement a more flexible approach without claiming that BSC could improve patients QoL, as it is not observed within the study. For patients who progress before 18 years of age, thus discontinuing selumetinib, utility decreases from that of a treated patient to that of an untreated patient over a five-year period and remains constant afterwards. When patients in the selumetinib arm reach 18 years of age, their utility value remains constant throughout the rest of the time horizon. This assumption is based on data from the Natural History study, which demonstrated that PN volume growth is rapid in childhood but stops or slows as a patient reaches adulthood (Figure 18). Figure 18 shows the percentage change in target PN volume of the individual patients of the natural history cohort over 5 years at different age intervals (<1; 1 - <7; 7 - <12; 12 - <16; ≥16 years old). It can be observed that when patients are in their early childhood, they experience a greater percentage change (increase) in their target PN volume, which translates into PN growth. On the contrary, when patients get older and reach adulthood, they experience a lower or no percentage change in their target PN volume, which translates into a PN growth plateau and disease stabilization.

Nonetheless, to acknowledge the small risk of progression after the age of 18, the analysis includes a continued risk of progression up to the age of 24. Before the threshold of 18 years, patients in the selumetinib arm will experience a yearly risk of progression rate of 5.6% while patients in the BSC arm will follow a lognormal distribution in line with the standard methodology proposed by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 [88]. After the age of 18, an annual progression rate of 1.35% is applied for both the selumetinib arm and BSC arm. Based on Danish clinical practice, the most important risk factor for tumour progression is patient's age. A very young child with a large tumour is usually considered a patient at risk. Nonetheless, there are no insights on the location of the PN concerning the progression, and whether they progress constantly highly depend on the individual patient [52].

In the paediatric NH age matched cohort, 85% of patients experienced tumour progression over three years [86]. This equates to a rate of progression of 28.3% per year. As paediatric patients experience a tumour growth rate that is around 21 times higher than adult patients (14.6% per year versus 0.7% per year) [89], the simple calculation of 28.3%/21=1.35% was used to estimate a progression rate of 1.35% per year for patients aged between 18 and 24 years. Tumour growth rate is even lower in older adult patients, and it is assumed that any further PN progression would stop by the age of 24, in both the selumetinib and BSC arms.

Figure 18. Change in PN volume growth – individual patient profiles over 5 years



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 Danish life tables. A standardised mortality rate (SMR) was applied to account for a reduced life expectancy associated with NF1-related comorbidities to accurately capture costs and benefits for the entire model time horizon.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The input data used in the base case was taken from the clinical trial SPRINT [90]. Furthermore, where needed, data was extrapolated based on goodness-of-fit statistics and clinical plausibility. A summary of included inputs is presented in Table 18.

Table 18. Estimates applied in the heath economic model

Variable	Value	Source
Patient characteristics		
Mean starting age	6.3	NF1 Danish study
Mean body surface area at entrance	0.896	Calculated through linear regression algorithm [91]
Sex (male %)	38%	NF1 Danish study
Survival analysis		
PFS survival model	Selumetinib: Simple probability of progression with annual rate of 5.6% until age 18, 1.35% until 24, 0% afterward. BSC: lognormal distribution until 18, 1.35% progression rate until 24, 0% afterward.	SPRINT + KOL validation[52]
Treatment duration	Weibull	Natural History study from SPRINT
Cycle length	1 year	Assumption
Time Horizon	100 years	Assumption - lifetime
Selumetinib treatment duration	~ 12 years/Once the patients reached adulthood	SPRINT + KOL validation [52]
Dose interruption weighting	7.7% per annum	Assumption based on SPRINT data
Adverse events		
Diarrhoea	16%	SPRINT
Vomiting	8%	
Pyrexia (Fever)	6%	
Hypoxia	8%	
Paronychia	8%	
Dermatitis acneiform	6%	
Quality of life		SPRINT + KOL validation [52] and Assumption
Selumetinib (PFS)	0.740	
BSC (PFS)	0.625	
Untreated (PD)	0.510	

Years to achieve HRQoL after treatment	1 year	Assumption based on SPRINT
Years to revert to baseline (untreated) HRQoL after treatment discontinuation	5 years	
SMR for NF1	2.02	Duong et al. 2011 [92]

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

In line with the data from the study performed by the two national centres of NF1 expertise in Denmark [50] the population used in the model concerns paediatric patients who have NF1 and symptomatic, inoperable PN, aged 2 to 18. The key baseline patient parameters from the study are presented in (Table 19). Patients had a mean age of 6.3 years when treatment started, and a body surface of 0.896 m^2calculated through a linear regression algorithm.

Table 19. Patient population

Patient population Important baseline characteristics	Clinical documentation	Used in the model	Danish clinical practice
Mean Age at treatment start (SD)	6.3 (3.7) [50]	6.3 (3.7)	[50]
Sex (Male %)	38% [50]	38%	[50]
Body surface area	0.896 m^2 [50]	0.896 m^2	[50]

8.2.2.2 Intervention

There is currently no medical treatment for NF1 PN: treatments with traditional antineoplastic agents such as radiotherapy and chemotherapy are unsuitable due to the risk of PN malignant transformation, and surgical removal of these tumours often remains incomplete, or it is avoided due to excessive risk.

Selumetinib is an orally available, potent, and selective, non-ATP-competitive mitogen-activated protein kinase (MEK) 1/2 inhibitor. Treatment with selumetinib aims to control and reduce the volume of PN.

Intervention in the clinical documentation submitted:
The key clinical documentation in this health economic assessment is the clinical trial SPRINT [90], paired with baseline characteristics sourced from the relevant Danish study [50].
Inputs used in the cost-effectiveness analysis are primarily informed by the SPRINT trial and clinical literature. See Section 7 for clinical details of SPRINT and Section 8.2.2.1 on patient population above.

Intervention as in the health economic analysis submitted:
The dosing regimen for selumetinib used in the analysis was derived from the SPRINT Phase 2 Stratum I trial paired with the Danish patients' characteristics. Selumetinib was administered according to BSA (body surface area) dosing (25 mg/m^2 twice daily- BID), with doses rounded to the nearest 5–10 mg using a dosing nomogram (Table 20). The maximum single dose was 50 mg.

In the base-case analysis, patients enter the model with a mean BSA of 0.896 m^2calculated through a linear regression algorithm that estimates BSA based on age and gender split [91] aligned with the Danish cohort. BSA was then assumed to increase annually according to the same linear regression algorithm [91]. The analysis can also predict the starting and future BSA as patients age using the linear regression algorithm. Patient's baseline data based on SPRINT clinical trial were explored in a scenario analysis.

The parameters used for the linear regression are presented in Table 21 and the linear regression plotted against the Danish study data is presented in Figure 19. BSA increases year by year until the cohort reaches 18 years of age. At this point, the BSA is assumed to remain constant for dosing purposes.

Furthermore, duration of exposure data from the SPRINT study suggest that actual treatment days with selumetinib totalled 669.6 compared with a total treatment duration of 725.7 days. It could therefore be inferred that over the duration of the analysis, the delivered selumetinib dose could be reduced by approximately 7.7% per annum to account for dose interruptions and reductions. The base case analysis included this dose reduction.
Posology of the intervention are based on SPRINT and are showed in Table 22.

Table 20. Dosing nomogram from SPRINT used in the health economic analysis

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
Dose required (mg) (25 mg/m^2/dose)	20 (morning) 10 (evening)	20	25	30	35	40

Table 21. BSA linear regression parameters

Parameter	Value
Age	0.0847
Constant	0.3874

Figure 19. Fit of linear regression to BSA data over time from the Danish study

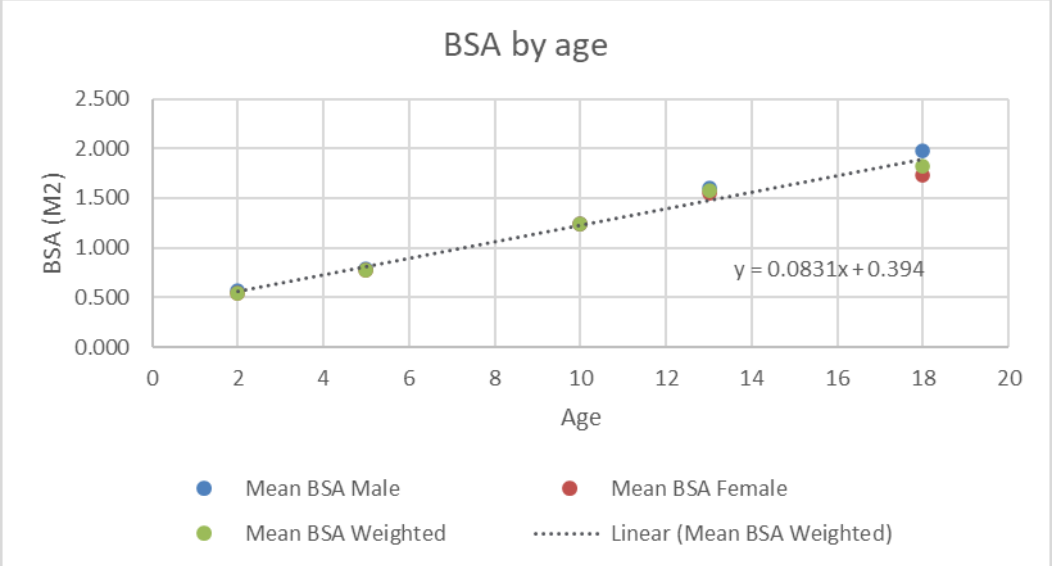


Table 22. Intervention

Intervention - selumetinib	Clinical documentation [90]	Used in the model	Expected Danish clinical practice
Posology	25 mg/m² twice daily, orally, based on BSA.	25 mg/m² twice daily, orally, based on BSA.	Not available
Length of treatment	Until patients reach adulthood.	TTD Based on the extended mean of TTD in SPRINT.	Not available
Dose discontinuation	7.7% per year.	7.7% per year.	Not available
Criteria for discontinuation	Adulthood and/or PN stabilization	Adulthood and/or PN stabilization	Not available
The pharmaceutical's position in Danish clinical practice	Symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.	Symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.	Not available

8.2.2.3 Comparators

The comparator considered within the health economic analysis is BSC as mentioned in Section 5.2.2, which consists of symptomatic treatment (e.g., analgesics to manage pain) or surgical treatment to remove or reduce the size of the PN. The specific nature of BSC varies due to the wide range of PN-related symptoms. As a patient's PN develops and the symptoms progress, symptomatic treatments may become increasingly ineffective. A summary of characteristics of BSC is presented in Table 23.

Table 23. Comparator

Comparator - BSC	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Not Available	Not Available	Not Available
Length of treatment*	Life	Life	Life
The comparator's position in the Danish clinical practice	Symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.	Symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.	Symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.

*BSC is not explicitly defined in the model as it is assumed that it is used equally for the two arms and thus the cost cancels out in the analysis.

8.2.2.4 Relative efficacy outcomes

The primary clinical outcome captured in the SPRINT trial used to assess selumetinib efficacy was PN volume change from baseline. In the SPRINT trial, most of the patients receiving selumetinib demonstrated decreases in target PN volume over time. However, the SPRINT trial enrolled a small number (n=50) of highly heterogenous patients who had a broad range of baseline target PN volumes (5.6 to 3,820.0 mL), target PN locations and baseline ages (3.5 to 17.4 years old) [93]. As a consequence of the limited availability of data and its heterogeneity, it was not possible to establish a robust association between target PN volume or another surrogate endpoint and HRQoL.

Therefore, the primary endpoint used in this analysis relies on the progression free survival (PFS) under treatment to assess the efficacy, since progress free status is a relevant factor regarding treatment decisions in Denmark. At 3 years since the start of treatment with selumetinib, median PFS was not reached, with a probability of being progression-free of 84%, hence parametric extrapolations were not used given the immaturity of the data. Nonetheless, to provide a measurement of efficacy which reflected the clinical trial's data, the cumulative probability of progression on selumetinib of 16% by three years was included, for an annual progression rate of 5.6% applied until patients reach adulthood in the model, followed by a rate of 1.35% until the age of 24, and 0% afterward.

Table 24. Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint: Progression free survival (PFS)	At 3 years from the beginning, 84% of patients were progress free, corresponding to an annual rate of progression of 5.6%	Annual rate of disease progression of 5.6% until age of 18, 1.35% until age of 24, 0% afterward.

Table 25. Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: Progression free survival	Defined as the cumulative probability of progression on selumetinib from the time of randomization to documented disease progression.	PFS represents a relevant outcome measure with regards to treatment of NF1 inoperable PN. Based on it,	Relevant.

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
		treatments may be prioritize over others.	

8.2.2.5 Adverse reaction outcomes

Adverse events (AEs) data from the SPRINT trial were included in the model as a base case. The most commonly reported AEs of Grade ≥3 that occurred during SPRINT were diarrhoea (16%), vomiting (8%), pyrexia (fever) (8%), hypoxia (8%), paronychia (6%) and dermatitis acneiform (6%) [94]. AEs reported in SPRINT and included in the analysis are presented in Table 26. It was assumed that there are no adverse events associated with best supportive care. A scenario analysis without the inclusion of AEs is explored in section 8.7.1.

Selumetinib monotherapy has a generally predictable and manageable safety profile in paediatric patients with NF1 PN, and AEs are usually mild or moderate in severity [94]. It can therefore be assumed that AEs have a minimal impact. For completeness, AEs-associated costs and disutilities were explored in a scenario analysis. The discontinuation rate due to AEs was not considered separately and was reflected in the overall TTD data.

Table 26. Adverse reaction outcomes for selumetinib

Adverse reaction outcome	Frequency in patients (n/N)	Mean duration, days (SD)
Diarrhoea	16% (8/50)	4.5 (4.50)
Vomiting	8% (4/50)	1.4 (0.55)
Pyrexia (Fever)	8% (4/50)	2.4 (1.14)
Hypoxia	8% (4/50)	5.2 (3.06)
Paronychia	6% (3/50)	16.8 (9.36)
Dermatitis acneiform	6% (3/50)	114.50 (76.59)

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

The inputs regarding effectiveness for selumetinib were sourced from the pivotal trial SPRINT. The main input concerning effectiveness used in the health economic analysis was PFS. The overall population from the SPRINT trial was used to conduct the survival analyses for PFS.

8.3.1.1 Progression free survival

PFS was used to determine whether patients in the selumetinib arm were clinically benefiting from treatment (as modelled by maintained improvement in QoL), irrespective of whether they were still on treatment (determined based on time to discontinuation [TTD]). In the base case, the PFS data from SPRINT was used; the cumulative probability of progression, on selumetinib, of 16% by three years was included, for a constant annual progression rate of 5.6% applied up until patients reach age of 18, assuming an exponential distribution. This is followed by a short period where the

progression rate drops to 1.35% until age 24, to account for potential PN growth after adulthood. An option for using parametric distributions has also been included in the model. For the BSC arm, PFS was modelled using standard parametric functions. Among the parametric distributions explored, the lognormal distribution had the best fit as determined using goodness-of-fit statistics. PFS for BSC was assumed to follow the lognormal distribution until patients reach the age of 18, after which point the progression rate of 1.35% is applied, representing the stabilisation of PN growth seen in adulthood, an assumption further supported by clinical evidence and the NH study [71, 86]. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) for each distribution used in the selumetinib and the BSC PFS arm are presented in Table 27 and Table 28, respectively.

Table 27. Selumetinib PFS goodness-of-fit statistics

Distribution	AIC	BIC
Exponential	43.61	45.52
Generalised gamma	38.54	44.28
Gompertz	41.46	45.29
Log-logistic	40.63	44.46
Lognormal	40.23	44.06
Weibull	40.70	44.53

AIC: Akaike information criterion, BIC: Bayesian information criterion

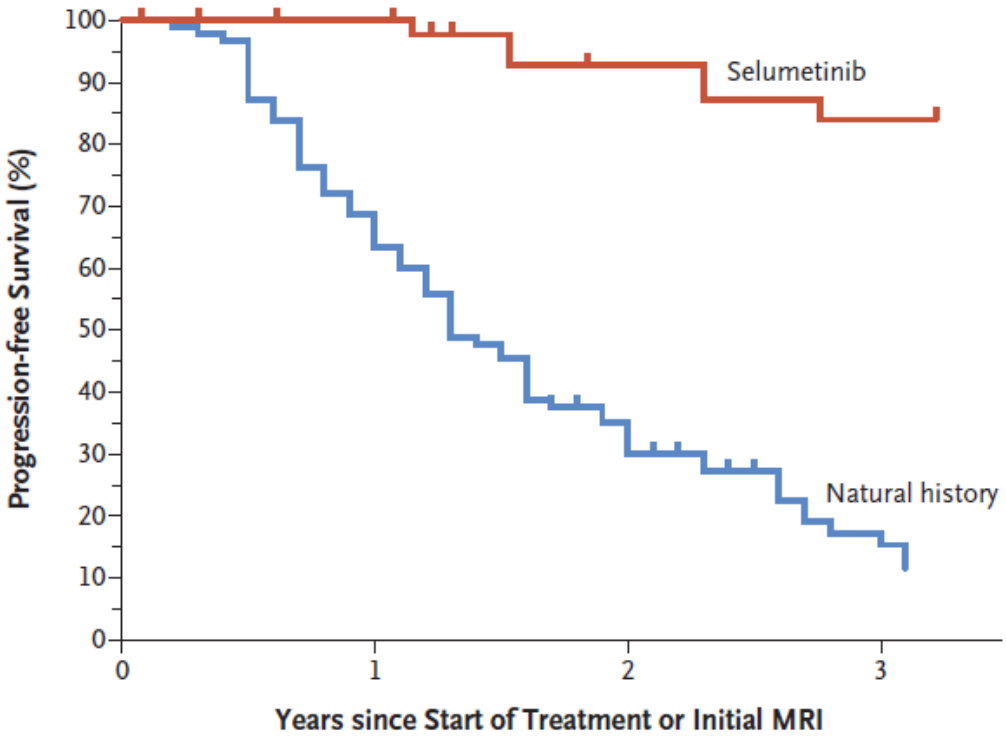
Table 28. BSC PFS goodness-of-fit statistics

Distribution	AIC	BIC
Exponential	610.11	612.64
Generalised gamma	588.93	596.49
Gompertz	609.67	614.71
Log-logistic	591.78	596.83
Lognormal	589.39	594.43
Weibull	601.6	606.64

AIC: Akaike information criterion, BIC: Bayesian information criterion

Given the clinical evidence presented in Figure 18, the assumption of constant risk of progression is rather conservative, since volume growth of PN is shown to decrease or stop over time. Due to the immaturity of the PFS data, parametric models were not used in the base case as most of the patients (~85%) had not progressed by year 3 of SPRINT. The naïve comparison with the NCI NH study revealed that the median PFS of the age-matched patients was 1.3 years (95% CI: 1.1-1.6) with a probability of being progression-free at 3 years of 15%, as it is illustrated in Figure 20. Modelled PFS and TTD are shown in Figure 21 and Figure 22 for selumetinib (both TTD and PFS) and BSC (only PFS), respectively.

Figure 20. PN progression–free survival during SPRINT compared with natural history of NF1



Number of patients at risk	Year 0	Year 1	Year 2	Year 3
Natural History age-matched cohort	65	43	21	15
Selumetinib-treated	50	41	16	0

The propensity score analyses exploring the comparison of PFS between selumetinib in the SPRINT study versus the NH study revealed that selumetinib treatment strongly reduced the risk of PN progression compared to no treatment. These results were consistent with and support the robustness of the naïve comparison to the age-matched cohort. Further details concerning the matching are described in Appendix F – External control: Natural History study propensity score matched analysis.

Figure 21. Progression free survival and time to treatment discontinuation for selumetinib

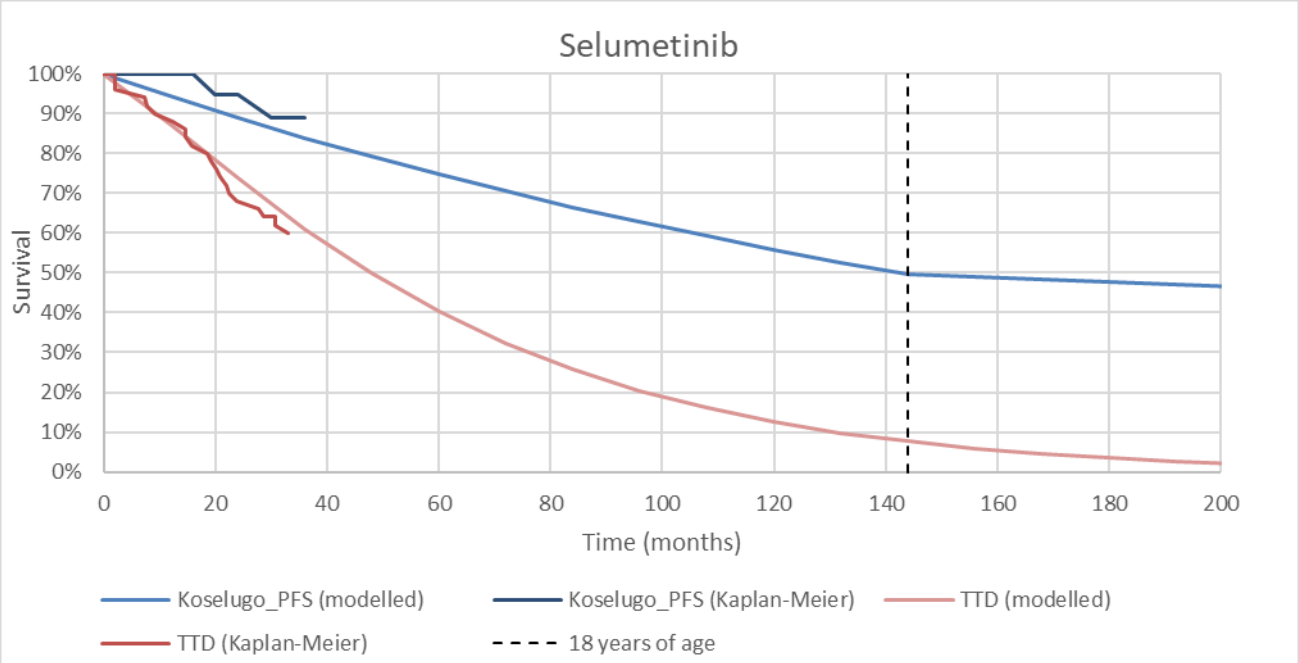
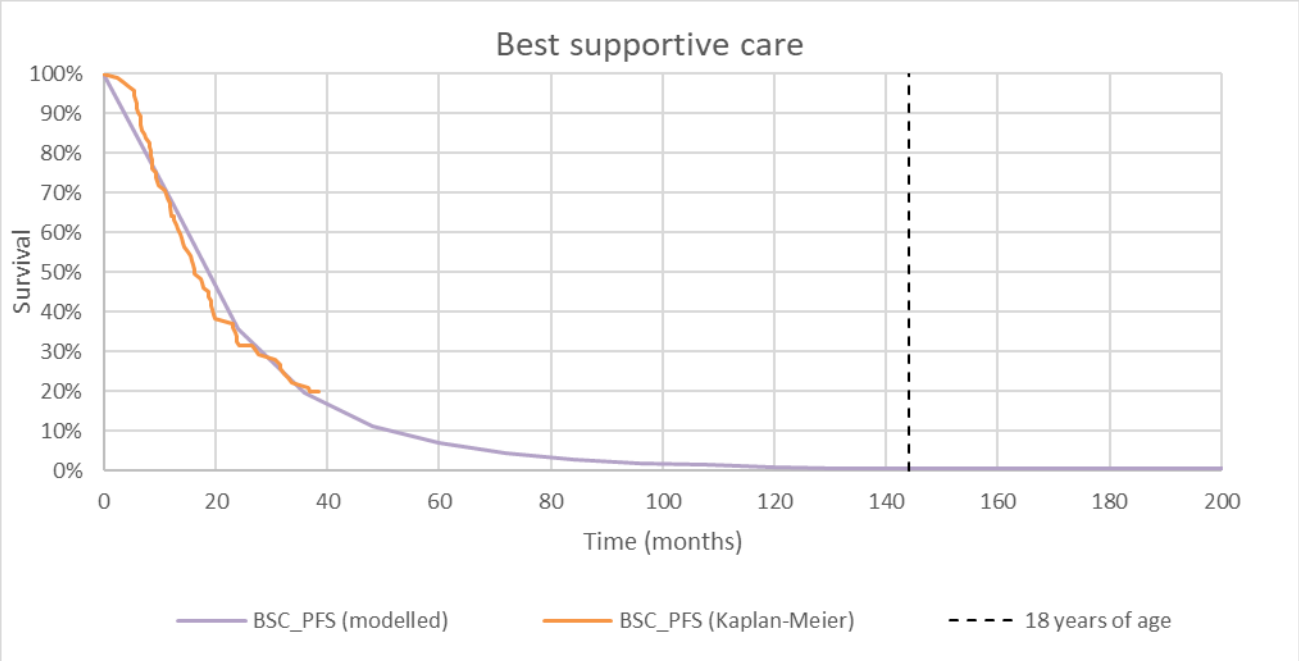


Figure 22. Progression free survival for best supportive care



Furthermore, in Table 29 a summary and overview of the PFS values used, and their relationship with the study data is described.

Table 29. PFS extrapolation overview

	Mean PFS	Modelled median PFS	Observed median from relevant study, years
Koselugo®(selumetinib)	35 years	12 years	NA[a]
BSC	2.7 years	3 years[b]	1.3 years [42]

[a]The median PFS has not yet been reached, with only 12% of patients experiencing disease progression (6/50)

[b]The model cycles are yearly, and due to the fast BSC progression, PFS shift to 61% to 32% from year 2 to year 3, therefore the reported value is an approximation.

8.3.1.2 Treatment duration

On model entry, 100% of 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 2 Stratum I. Six parametric distributions were explored to assess the most appropriate model for treatment duration (distributions, parameters and coefficients are displayed in Table 30).

Table 30. TTD model parameters

Distribution	Parameter	Coefficient
Exponential	Intercept	-4.3042
Generalised gamma	Mu	4.0399
	Sigma	0.2092
	Q	0.2478
Gompertz	Shape	0.0052
	Rate	-4.3944
Loglogistic	Shape	0.3094
	Scale	3.8999
Lognormal	Meanlog	3.9717
	Sdlog	0.3057
Weibull	Shape	0.1742
	Scale	4.1747

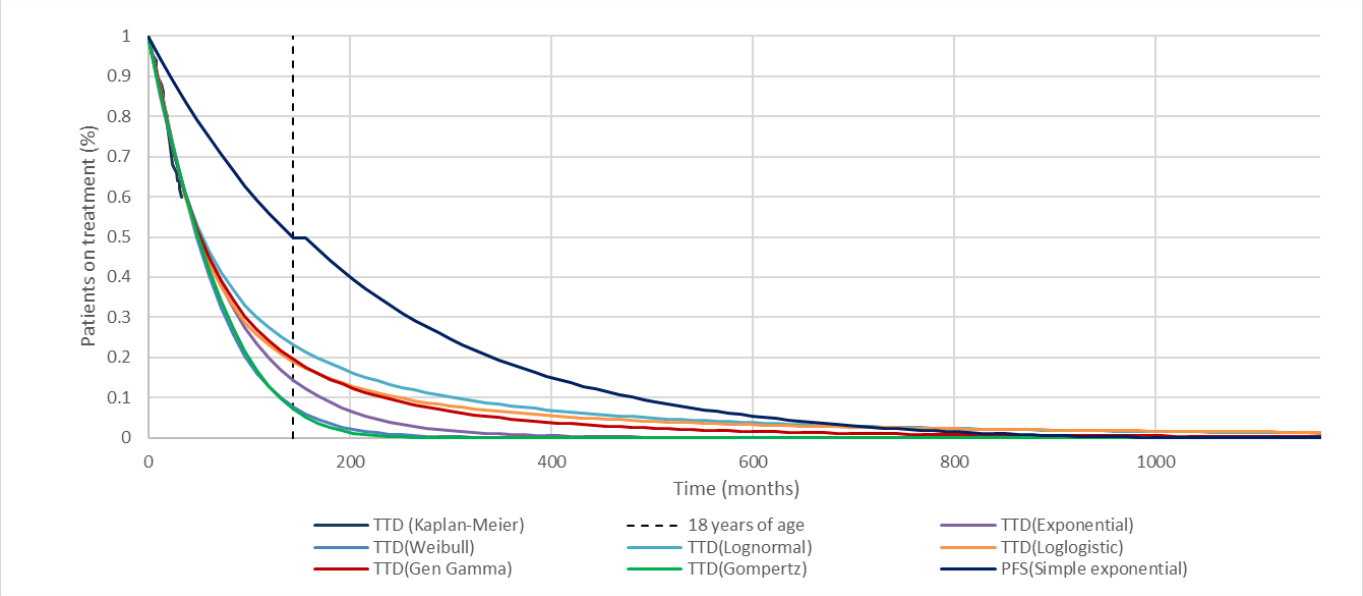
Selection of the most appropriate distribution was informed by goodness-of-fit statistics, visual inspection of the extrapolated curves against SPRINT Phase 2 Stratum I data and clinical plausibility. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) for each distribution are presented in Table 31.

Table 31. TTD model goodness-of-fit statistics

Distribution	AIC	BIC
Exponential	214.168	216.080
Generalised gamma	216.946	222.682
Gompertz	216.103	219.928
Log-logistic	214.946	218.770
Lognormal	215.007	218.831
Weibull	215.517	219.342

AIC and BIC values were very similar across all distributions, implying that the parametric models were similar in terms of statistical fit. Therefore, the selection was based on clinical plausibility. The extrapolated curves together with the TTD survival data from the SPRINT Phase 2 Stratum I are presented in Figure 23.

Figure 23. TTD parametric models



Data from the Natural History study demonstrated that PN volume stabilises as a patient reaches adulthood [90]. Consequently, as a patient reaches adulthood, discontinuation rates would likely be high as remaining on treatment would provide minimal benefit. Therefore, the Weibull distribution provides the most clinically plausible predictions as it results in the highest rate of discontinuation over the 100-year time horizon. The Weibull distribution was therefore used in the base case analysis. Other distributions were explored in scenario analyses. In Table 32, a summary and overview of the TTD values used described.

Table 32. TTD extrapolation overview

	Mean TTD	Modelled median TTD	Observed median from relevant study
Koselugo®(selumetinib)	5.6 years	4 years	NA[a]

[a]The median TTD was not reported in the study.

8.3.1.2.1 Treatment duration cap

PN volume growth is rapid in childhood but stops or slows as a patient reaches adulthood [90]. Given that the mean starting age in the model is 10.3 years (in line with SPRINT data), a treatment duration of approximately 8 years is likely to reflect the maximum duration in clinical practice. Consequently, the analysis includes the possibility to stop treatment with selumetinib after 8 years without waning of treatment effect. This was explored in a scenario analysis in Section 8.7.1.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

The SPRINT Phase 2 Stratum I trial assessed Health related quality of life (HRQoL) 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 [95]. However, there are no appropriate published, validated algorithms to map PedsQL values to EQ-5D index scores which are sufficiently comparable to be applied to the NF1 PN patient population.

Furthermore, the HRQoL data from SPRINT are only available for patients treated with selumetinib for up to 3 years of follow-up and no alternative utility values have been reported for NF1 PN patients. Given the rarity of NF1 PN, literature searches yielded no relevant utility data for paediatric and adult patients. As such, there are insufficient data to address the entire patient lifetime in a cost-effectiveness analysis of selumetinib compared to BSC. Therefore, alternative approaches to measuring HRQoL were required to conduct a robust analysis. A vignette-based time-trade-off (TTO)[96] study was performed to elicit utility weights for different health states associated with patients with NF1 PN. The study is described in Appendix K – HSUV related study.

The utility values used in the cost-effectiveness analysis were derived from the TTO study described in Appendix K – HSUV related study, with the exception of BSC PFS utility and are presented in Table 33. In the base case analysis, selumetinib patients start with the utility of an untreated patient (0.51) and, if the patient is being treated with selumetinib, they reach the utility value of a treated patient (0.74) over 1 year. On the other hand, if the patient is on the BSC arm but do not experience progression, a utility value of 0.625 will be used, which is a midpoint between the progressed and the selumetinib treated utility. For patients who discontinue treatment due to progression before 18 years of age, utility decreases from that of a treated patient (0.74), or from the BSC PFS (0.625), to that of an untreated patient (0.51) over a 5-year period and remains constant afterwards.

The rationale behind the choice of assigning a lower value for PFS in the BSC arm is motivated by the absence of observed PN volume reduction for patients treated with BSC. Across the natural history study, a median growth rate of 15.9% per year was observed (lower quartile 10.1%, upper quartile 28.0%) [8]. This assumption is further consolidated by the fact that the entirety of PN included in the Gross et al. 2018 analysis, which had associated morbidity present at baseline, still had a morbidity present at last assessment.

When patients in the selumetinib arm reach 18 years of age, their utility value remains constant throughout the rest of the time horizon; this assumption is based on data from the Natural History study, which demonstrated that PN volume growth stops or slows as a patient reaches adulthood [90]. This assumption was validated by Danish clinical experts [52].Patients in the BSC arm are assigned to PFS utility (0.625), and after progression, they maintain the utility of a progressed patient (0.51) throughout the whole analysis.
Moreover, the assumption that HRQoL in 'progressed' patients (i.e., those without selumetinib or BSC progressed) remains stable for the model duration is 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 potentially experience a decrease in HRQoL. The same conservative stance is assumed in case of BSC PFS patients, which will still suffer from PN symptoms, which explains why the PFS utilities are different by treatment arms. In SPRINT, patients receiving selumetinib had an improvement in utility, as the model assumes that unless patients progress, the improvement will persist (with age adjustment over the time horizon). If patients discontinue selumetinib before adulthood, their tumour will begin to regrow and their utility value will decrease, trending back to the adult value. The rate of decrease will be the same as for BSC patients. The value will then remain constant throughout adulthood, i.e. there may be a residual benefit of selumetinib through reduced tumour volume. For patients receiving BSC, PN volume will increase and QoL will decrease from the point of entry until adulthood, upon which tumour volume/QoL will stabilize and remain constant for the rest of the analysis. This assumption was validated by Danish clinical experts [52].

Furthermore, mortality within the model is based on adjusted all-cause mortality probabilities, stratified by age and gender from the 2020 Danish national life table [97]. The rate of all-cause mortality was adjusted for the decreased life expectancy linked to NF1/PNs. A targeted literature search identified a relevant study reporting a standardised mortality rate (SMR) for patients with NF1 [92]. The SMR was incorporated to accurately model the costs and effects for patients over their lifetime. The identified SMR for patients with NF1 is shown in Table 34.

Table 33. Utility values for PFS and PD

Status	Utility	Source
Progressed (Untreated)	0.510	
Progress free (Selumetinib)	0.740	
Progress free (BSC)	0.625	Assumption

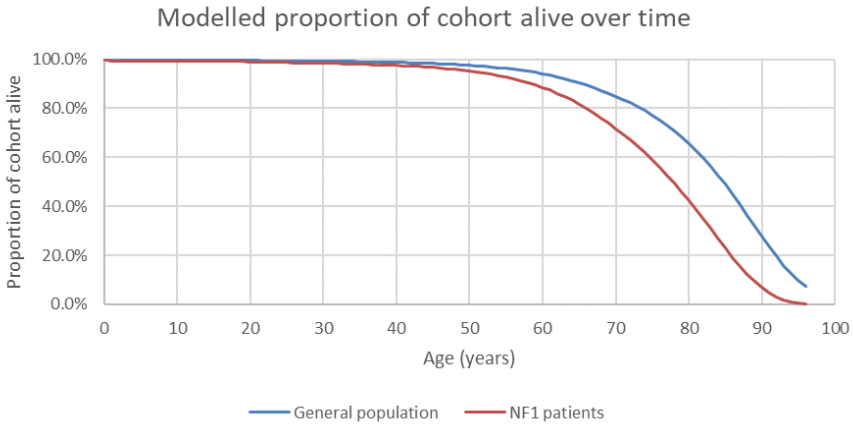
Table 34. SMR used to adjust all-cause mortality

SMR (95% CI)	Source
2.02 (1.6–2.6)	Duong et al, 2011 [92]

The SMR of 2.02 was applied to both the selumetinib and BSC arms, which is conservative. The impact of selumetinib on mortality was not considered in the model. Selumetinib is a disease modifying treatment and may have an impact on the mortality rate of patients with NF1 PN. However, due to data limitations it was not possible to incorporate this into the analysis: SPRINT was not designed to evaluate the impact of selumetinib on mortality due to its small cohort and short duration. Moreover, according to Danish clinical expert, there would be no change on mortality between the two treatments arms based on the available data [52].
Nonetheless, a decreased SMR of 1.5 for patients treated with selumetinib was explored in the scenario analyses. This value is an assumption based on a simple mean between the 2.02 and 1.0 SMR of NF1 and the background population.

Figure 24 shows the proportion of the cohort alive over time when the SMR for patients with NF1 is applied.

Figure 24. Proportion of the cohort alive over time when the SMR for patients with NF1 is applied



8.4.2 Disutility due to adverse events

Disutilities associated with adverse events were included within the model. The frequency of AEs experienced in patients treated with selumetinib, based on SPRINT trial data, was used to calculate a one-off AE disutility for selumetinib (-0.03441). Disutilities occurring as a result of AEs were applied in the first model cycle only, as it is reasonable to assume that treatment-related AEs are most likely to occur shortly after initiating a new therapy. The AE disutilities and associated frequencies used to estimate treatment-related disutilities used in the model are presented in Table 35 An additional scenario without the AEs disutility was explored in the scenario analysis.

Table 35. Adverse events disutility

Adverse event	Disutility	Mean Duration, days (SD)	Source
Diarrhoea	-0.044	4.5 (4.50)	[98]
Vomiting	-0.095	1.4 (0.55)	[99]
Pyrexia (Fever)	-0.0325	2.4 (1.14)	[100]
Hypoxia	-0.11	5.2 (3.06)	[101]
Paronychia	-0.049	16.8 (9.36)	Assumed to be the same as fatigue [99]
Dermatitis acneiform	-0.085	114.50 (76.59)	Assumed to be the same as edema [102]

8.4.3 Age-adjustment of the quality of life

In the base case analysis, the methodology used for the age-adjustment consisted in using the Danish general population utilities stratified by age groups to calculate the age-dependent multipliers. The age-dependent multipliers were then used to adjust the individual's undiscounted utility levels each cycle according to their age. Table 36 shows the Danish

general population utility values stratified by age groups and Table 37 shows the matrix with the age-dependent multipliers used in the model.

Table 36. Danish general population utility values stratified by age groups

Age group	Utility values
0-17	1
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818
70-79	0.813
80+	0.721

Source: DMC [97].

Table 37. Matrix containing the age-dependent multipliers used in the Danish setting

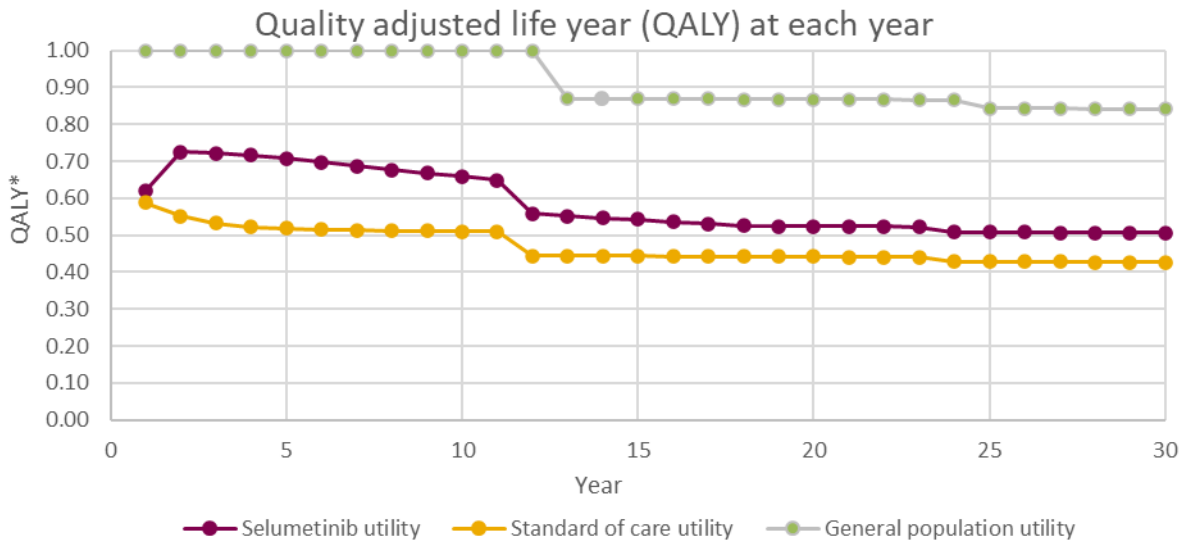
Age group and age-dependent multipliers	0	18	30	40	50	70	80
0	1	0,871	0,848	0,834	0,818	0,813	0,721
18		1	0,97359	0,95752	0,93915	0,93341	0,82778
30			1	0,98349	0,96462	0,95873	0,85024
40				1	0,98082	0,97482	0,86451
50					1	0,99389	0,88142
70						1	0,88684
80							1

Alternatively, the utility values for all patients could be further modified by a linear regression algorithm from Ara and Brazier (2010), which accounts for age-related disutility [103]. The regression algorithm to calculate general population utility as the population ages is the following:

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

The total accrued utility over the first 30 years of the model is shown in Figure 25.

Figure 25. Age adjusted utility values for the first 30 years of the model



Note: The QALY starts at year 1 in the graph, which is the time required for the treated utility to be in place

This approach may underestimate the true impact of selumetinib on QoL:

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 partial response) shows a clear association with an increase in the number and severity of PN-associated morbidities [8, 57, 104]. Therefore, it is reasonable to assume that increased PN volume will likely negatively impact HRQoL, irrespective of location.
Nonetheless, Ara and Brazier age adjustment is explored in the scenario analysis in Section 8.7.1.

8.4.4 Health state utility values used in the health economic model

In order to measure HRQoL, a vignette-based time-trade-off (TTO) study was performed to elicit utility weights for different health states associated with patients with NF1 PN. The study is describedin Appendix K – HSUV related study. The utility values associated with health states are reported in Table 33.

For the selumetinib PFS health state, which consistend in patients being treated with selumetinib over 1 year, the utility value was estimated to 0.74. The estimate was derived by clinical trial data, from the relevant population with the relevant treatment. For the BSC PFS health state, the utility value was estimated at 0.625 through the assumption of mid point value between the selumetinib PFS and the PD utility.

For the progressed health state, which the utility value was estimated to 0.51, and remain costant after adulthood is reached.

Furthermore, utility were age-adjusted, and adverse events are accounted for in the cost-effectiveness analysis; the model itself offers the possibility to expand further on the base case scenario, which was deemed to be the most appropriate to reflect current Danish clinical practice.

8.5 Resource use and costs

As selumetinib is expected to be provided in conjunction with BSC, no resource use or costs were considered as there would only be negligible incremental difference between selumetinib and BSC.

Table 38 below presents the drug prices of selumetinib in Denmark. The dosing nomogram with BID doses, and the correspondent cost per day are presented in
Table 39, while the estimated cost per patient calculations used in the model are shown in Table 40

It was assumed that NF1 patients with inoperable PN are assessed frequently by healthcare professionals (HCPs) throughout the year. Therefore, no incremental clinical contacts were assumed for the administration and monitoring of patients receiving selumetinib or the best supportive care (BSC). Consequently, no administration costs were considered in the analysis.

Costs associated with adverse events were included in a scenario analysis and are presented in Table 45. The frequency of AEs experienced in patients treated with selumetinib – based on SPRINT trial data – was used to calculate a one-off AE cost for selumetinib (DKK 8,155.44). Costs occurring as a result of AEs were applied in the first model cycle only, as it is reasonable to assume that treatment-related AEs are most likely to occur shortly after initiating a new therapy. They are presented in Table 41.

Table 38. Unit cost for Intervention (selumetinib))

Drug	Strength (mg)	Pack size	Unit cost (DKK) – AIP	Source
Selumetinib	10 mg	60	35,708	AstraZeneca
Selumetinib	25 mg	60	89,270	AstraZeneca

At the time of submission of this final application, Koselugo® is not officially listed in www.medicinpriser.dk and prices of the two strengths are therefore not finally confirmed. An agreement between Lif and the government (ends April 2023) request the list prices are lowered with 2.5 % according to a specific timeline. Next reduction is October 2022 and then again in February 2023. We expect this agreement to be extended/renewed and will include one more reduction of 2.5 % in October 2023 and then again in October 2024 and 2025.

Table 39. Dosing nomogram and cost per day

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 mg (morning) 10 mg (evening)	20 mg (BID)	25 mg (BID)	30 mg (BID)	35mg (BID)	40 mg (BID)	45 mg (BID)	50 mg (BID)
Cost per day (DKK)	1,785.40	2,380.53	2,975.67	3,570.80	4,165.93	4,761.07	5,356.20	5,951.33

Table 40. Estimated cost per patient for treatment with selumetinib

BSA (m^2)	Dose (mg)	Cost/day (DKK)	Cost/annum (DKK)
0.55-0.69	20 then 10	1,785.40	601,705.63
0.70-0.89	20 (BID)	2,380.53	802,274.18
0.90-1.09	25 (BID)	2,975.67	1,002,842.72
1.10-1.29	30 (BID)	3,570.80	1,203,411.27
1.30-1.49	35 (BID)	4,165.93	1,403,979.1
1.50-1.69	40 (BID)	4,761.07	1,604,548.35
1.70-1.89	45 (BID)	5,356.20	1,805,116.90
1.90-1.94	50 (BID)	5,951.33	2,005,685.44

Table 41. Healthcare utilization inputs for the management of adverse events

Input	Cost (DKK)	Comment/assumption	Reference
Diarrhoea	6,756	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	[105]
Vomiting	6,756	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	[105]
Pyrexia (Fever)	49,079	18MP03 Feber af ukendt årsag, med biopsi og/eller scopi	[105]
Hypoxia	3,319	33PR01 Hyberbar iltbehandling	[105]
Paronychia	19,518	09MA03 Lettere eller moderat hudsygdom, u. kompl. bidiag.	[105]
Dermatitis acneiform	19,518	09MA03 Lettere eller moderat hudsygdom, u. kompl. bidiag.	[105]

Diarrhoea

The cost of management of diarrhoea was applied for every occurrence. The management was assumed to be the same as the management of inflammation of the esophagus, stomach and intestines (complicated). The cost of DKK 6,756 was derived from the Danish DRG list [105].

Vomiting

The cost of management of vomiting was applied for every occurrence. The management was assumed to be the same as the management of inflammation of the esophagus, stomach and intestines (complicated). The cost of DKK 6,756 was derived from the Danish DRG list [105].

Paronychia

The cost of management of paronychia was applied for every occurrence. The management was assumed to be the same as the one concerning mild or moderate skin disease. The cost of DKK 19,518 was derived from the Danish DRG list [105].

Dermatitis acneiform

The cost of management of paronychia was applied for every occurrence. The management was assumed to be the same as the one concerning mild or moderate skin disease. The cost of DKK 19,518 was derived from the Danish DRG list [105].

Pyrexia

The cost of management of fever was applied for every occurrence. The management was assumed to be the same as the one concerning fever of unknow reason for those under age of 18. The cost of DKK 49,079 was derived from the Danish DRG list [105].

Hypoxia

The cost of management of hypoxia was applied for every occurrence. The management was assumed to be the same as the one concerning hyperbaric oxygen therapy. The cost of DKK 19,518 was derived from the Danish DRG list [105].

No other costs were considered in the analysis. It was assumed that the relative impact of treatment with selumetinib on the indirect costs (productivity loss) a patient or a parent/caregiver may experience would be minimal compared to the acquisition costs of selumetinib. Consequently, they were conservatively excluded from the analysis as the associated impact on the final ICER is likely to be small.

8.6 Results

8.6.1 Base case overview

An overview of the base case is resented in Table 42.

Table 42. Base case overview

Setting	Value/choice
Comparator	Best supportive care (BSC)
Type of model	Partitioned survival model
Time horizon	100 years (life time)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured using PedsQL 4.0 Generic Core Scales from SPRINT Phase 2 data[106]. A vignette-based time-trade-off (TTO) study was performed to elicit utility weights for the different health states.
Included costs	Pharmaceutical costs Adverse events
Dosage of pharmaceutical	Based on body weight and body surface area
Parametric function for TTD	Intervention: Weibull
PFS extrapolation	Intervention: Simple probability Comparator: Lognormal

8.6.2 Base case results

Table 43. Base case results

Per patient	Selumetinib	BSC	Difference
Life years gained (undiscounted)			
Total life years gained	69.93	69.93	0
QALYs			
Total QALYs	14.85	12.00	2.85
QALYs (adverse reactions)	0.00	0.00	0.00
Costs			
Total costs	4,920,425 DKK	0 DKK	4,920,425 DKK
Drug costs	4,912,270 DKK	0 DKK	4,912,270 DKK
Adverse reactions costs	8,155 DKK	0 DKK	8,155 DKK
Incremental results			
ICER (per QALY)	1,728,474 DKK		

The results of the base case show that the cost of an additional QALY gained from using selumetinib compared to best supportive care is predicted to 1,728,474 DKK, with an increased cost of 4,920,425 DKK and 2.85 additional QALYs and no additional life years compared to treatment with BSC. These results are likely to be conservative; the current assumption that HRQoL in 'progressed' patients (i.e., those without selumetinib) remains stable for the model duration is 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 potentially experience a decrease in HRQoL. The same issue applies for the PFS BSC arm since those patients will still suffer from marginal PN growth and associated morbidities. Additionally, as mentioned in Section 8.4.1, treatment with selumetinib could result in a decreased mortality rate compared to treatment with BSC alone.

Plots of QALYs accrued over time are presented in Figure 26 and Figure 27. Disaggregated costs are not presented as costs are only accrued in the selumetinib arm when patients are on-treatment.

Figure 26. BSC QALYs accrued over model time horizon

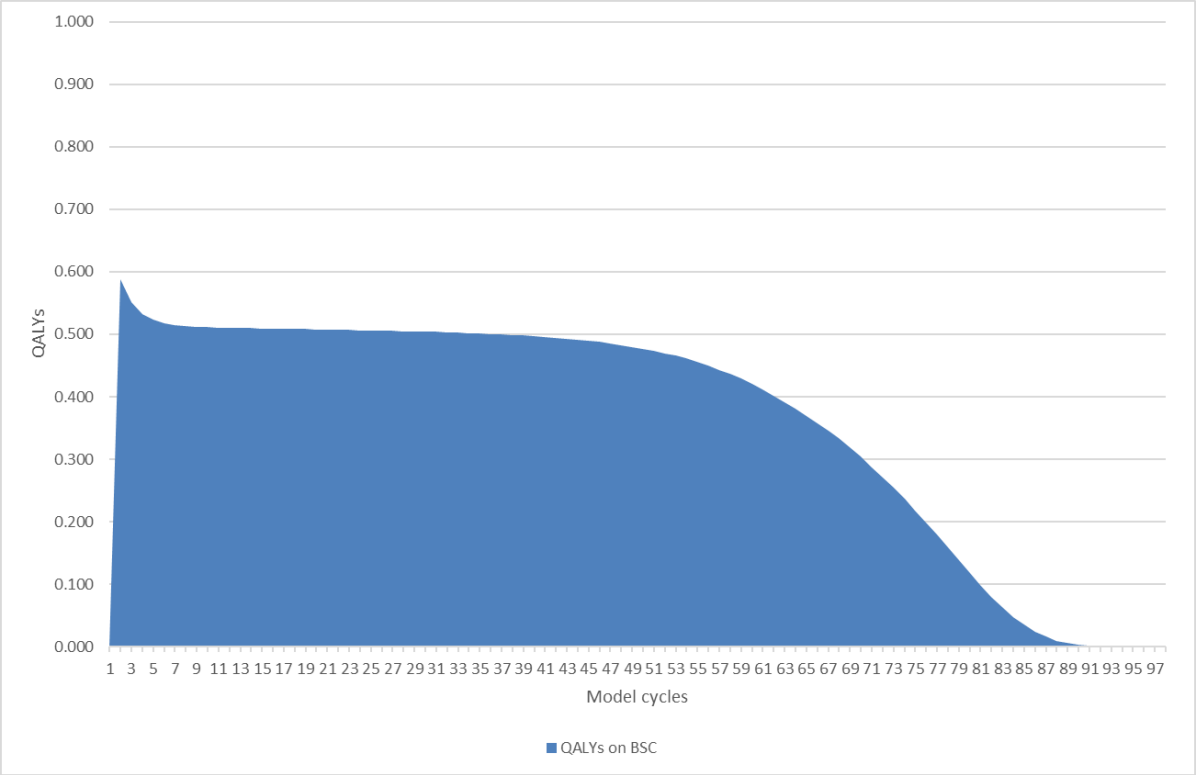
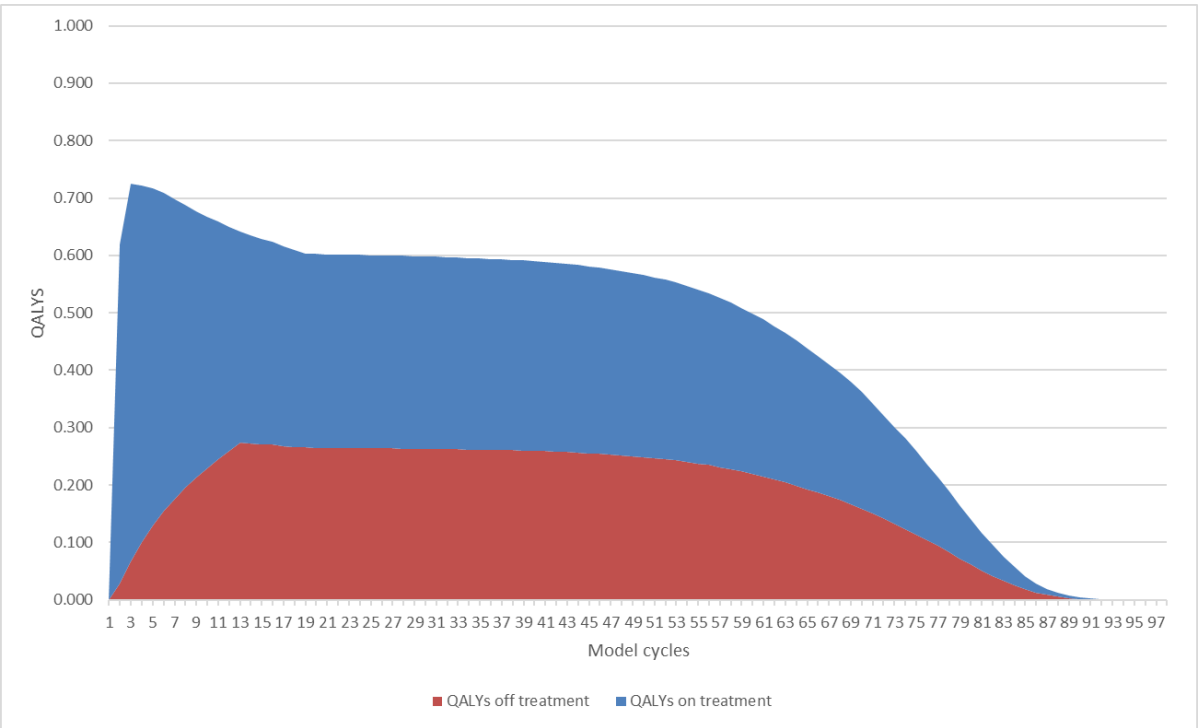


Figure 27. Selumetinib QALYs accrued over model time horizon



8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

The impact of individual parameters on the ICER was tested in one-way deterministic sensitivity analyses (OWSA). Parameter values were systematically and independently varied over a plausible range. For the 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 mean value. The ICER was recorded at the upper and lower values to produce a tornado diagram.

Figure 28 and Table 44 present the ten parameters that have the greatest impact on the ICER for selumetinib compared to BSC. The utility of the progressed patient is the most influential parameters, followed by cumulative probability of progression.

Table 45 presents a scenario analysis exploring the effect of different assumptions used in the analysis.

Table 44. Results of one-way deterministic sensitivity analysis (10 most influential parameters)

Parameter	Lower Bound	Upper Bound
BSC_PD utility (0.44 to 0.58; base case 0.51)	1,024,411.36 DKK	3,601,159.08 DKK
Cumulative_Prob_Prog (5.84% to 26.16%; base case 16.00%)	1,160,612.75 DKK	2,212,646.31 DKK
BSC - PFS: Lognormal: meanlog (3.177 to 4.766; base case 2.874)	1,638,279.28 DKK	2,621,759.00 DKK
Utility - Untreated (0.44 to 0.58; base case 0.51)	2,091,415.98 DKK	1,289,135.30 DKK
Utility - Treated (0.70 to 0.78; base case 0.74)	1,970,527.96 DKK	1,339,799.18 DKK
Dose interruption weighting (74% to 100%; base case 92%)	1,276,633.80 DKK	1,728,473.65 DKK
BSA_LinearReg_Age (0.068 to 0.102; base case 0.085)	1,375,664.93 DKK	1,822,259.93 DKK
Discount_Rate_Outcomes years 0-35 (2.80% to 4.20%; base case 3.50%)	1,420,589.76 DKK	1,777,617.36 DKK
BSA_LinearReg_Const (0.310 to 0.465; base case 0.387)	1,501,673.90 DKK	1,701,379.51 DKK
Average_Age (5.22 to 7.38; base case 6.30)	1,524,148.54 DKK	1,650,824.19 DKK

Figure 28. Tornado diagram

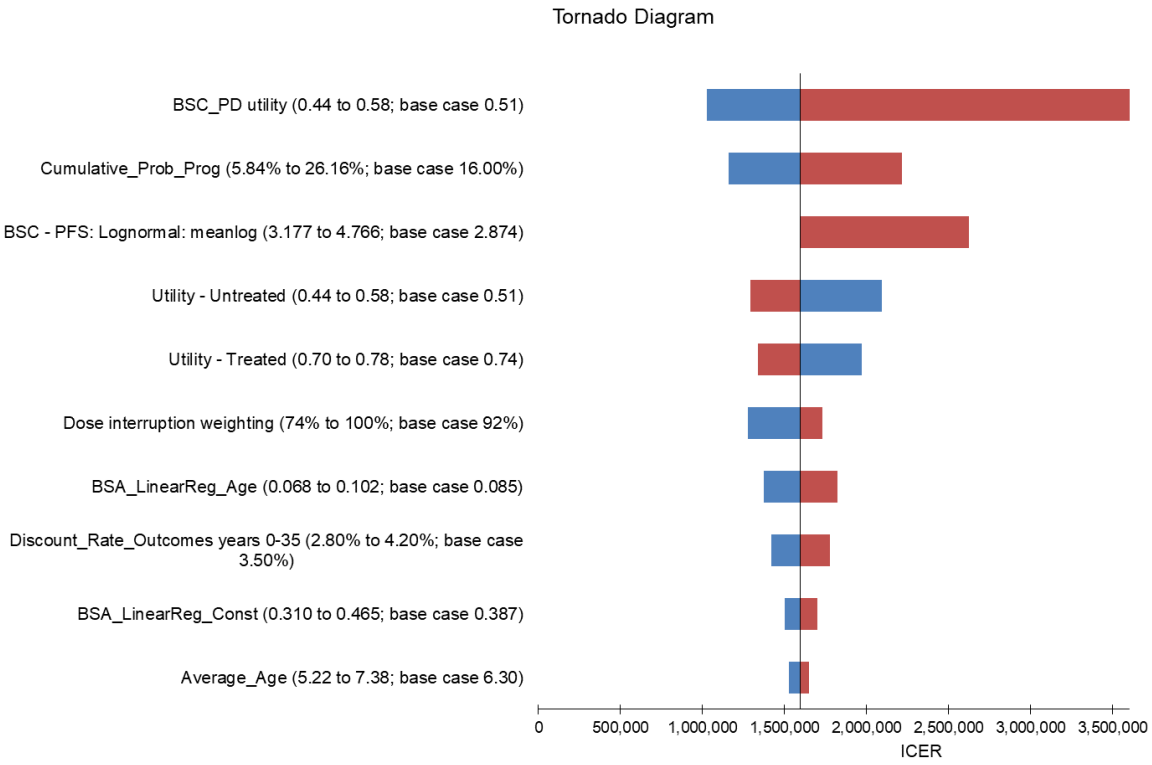


Table 45. Scenario analysis

Parameter	Base case	New value	Incremental cost	Incremental QALY	ICER
Base case			4,920,425 DKK	2.85	1,728,474 DKK
Time horizon	100	50 years	4,540,683 DKK	2.62	1,732,019 DKK
		30 years	4,539,998 DKK	2.22	2,042,972 DKK
		20 years	4,520,848 DKK	1.89	2,390,555 DKK
Starting age	6.3 years old (BSA calculated using linear regression)	10.3 years old (BSA calculated using linear regression)	5,663,780 DKK	3.20	1,771,823 DKK

Starting age	6.3 years old (BSA calculated using linear regressio n)	10.3 years old (BSA calculated from SPRINT)	5,176,834 DKK	3.20	1,619,489 DKK
Include AEs	Included	Not included	4,532,529 DKK	2.88	1,573,195 DKK
Perspective	Payer	Societal: Caregiver disutility until patient reaches 18 years of age Number of caregivers to be considered: 1.1	4,920,425 DKK	2.85	1,728,474 DKK
Perspective	Payer	Societal: Caregiver disutility (absolute reduction) until patient reaches 18 years of age Number of caregivers to be considered: 1.1	4,920,425 DKK	2.85	1,728,474 DKK
Perspective	Payer	Societal: Caregiver disutility (proportion change) for the duration of caregiver's life Number of caregivers to be considered: 1.1	4,920,425 DKK	2.85	1,728,474 DKK
Treatment duration cap	Not Included	8 years	3,683,305 DKK	2.85	1,293,891 DKK
Dose interruption weighting	92.3%	Not included	4,540,684 DKK	2.85	1,595,076 DKK
SMR	2.02	Not included	4,922,071 DKK	2.91	1,689,847 DKK

Age-adjusted utilities	Yes	No	4,920,425 DKK	3.12	1,579,447 DKK
Years to achieve treated HRQL	1	2	4,920,425 DKK	2.75	1,787,579 DKK
Years to revert to untreated HRQL	5	4	4,920,425 DKK	2.81	1,751,842 DKK
Parametric models for time to discontinuation	Weibull				
		Exponential	6,229,111 DKK	2.85	2,188,196 DKK
		Gen.gamma	7,913,200 DKK	2.85	2,779,792 DKK
		Gompertz	4,896,375 DKK	2.85	1,720,025 DKK
		Loglogistic	8,200,742 DKK	2.85	2,880,801 DKK
		Lognormal	9,315,410 DKK	2.85	3,272,367 DKK
Age-adjusted utilities	Yes (DMC)	Yes (Ara & Brazier)	4,532,529 DKK	4,540,684 DKK	2.86
Differential SMR	No	Yes (SMR with selumetinib 1.50)	4,541,458 DKK	3.03	1,496,980 DKK
Years to revert to untreated HRQL	5	3	4,920,425 DKK	2.77	1,776,565 DKK
Years to revert to untreated HRQL	5	2	4,920,425 DKK	2.73	1,802,741 DKK
Years to revert to untreated HRQL	5	1	4,920,425 DKK	2.69	1,830,483 DKK
Progression after 18 years old	Allowed	Not allowed	4,920,425 DKK	3.27	1,502,700 DKK
Parametric model for BSC annual proression rate (≤18)	Lognormal	Exponential	4,920,425 DKK	2.84	1,733,163 DKK
		Gen.gamma	4,920,425 DKK	2.80	1,758,397 DKK

		Gompertz	4,920,425 DKK	2.86	1,717,987 DKK
		Loglogistic	4,920,425 DKK	2.83	1,736,303 DKK
		Weibull	4,920,425 DKK	2.87	1,716,711 DKK
		Simple probability	4,920,425 DKK	2.89	1,704,031 DKK
BSC PFS utility	0.625	0.74	4,920,425 DKK	2.71	1,813,370 DKK
		0.51	4,920,425 DKK	2.98	1,651,171 DKK

8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) tests the impact of second order uncertainty by random, simultaneous variation of the input parameters on the model. Second order uncertainty does not include cohort characteristics, which are part of first order uncertainty. Therefore, age, percentage males and BSA of the population at study entry were not included in the PSA.

PSA analysis was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions to estimate the cost effectiveness ratios. A Beta distribution was assigned to probabilities, proportions and utility data which take values between 0 and 1. A Gamma distribution was assigned to costs which take positive values and are likely to be positively skewed. The Alpha and Beta values of the distribution were estimated based on the mean and standard deviation associated with each parameter.

If the standard deviation was not available from the reporting study, then it was calculated based on the following assumption:

*= (Upper range – lower range)/(2*NORMSINV(0.975))*

The upper and lower ranges were based on CIs when reported and if not, they were based on a variation of +/- 20%.

The parameters for the Weibull distribution were sampled using the variance-covariance matrix for the parametric model coefficients. The coefficients were not varied independently and the correlation between the variables was preserved using a Cholesky decomposition.

It should be noted that coefficients for the utility equation to adjust for age, and the coefficients for the BSA equation were sampled independently in the PSA. While the coefficients are likely to be correlated there are limited data available in the respective sources to facilitate this. The impact on the results is unlikely to be significant.

A total of 10,000 Monte Carlo simulations were recorded. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated. The former shows the distribution of incremental cost and benefits under uncertainty and the latter the likelihood of being cost-effective at given acceptability thresholds. Given the level of uncertainty regarding some inputs, only those where reasonable estimates of variance exist were included. The number of "unknown unknowns" makes performing a traditional fully comprehensive PSA challenging as there are important areas of structural uncertainty that cannot be explored. The PSA is expected to be limited in its usefulness but was included for completeness. The mean ICER at the end of 10,000 simulations was DKK 1,644,122 DKK.

Figure 29 presents the CEP. The spread of the points horizontally illustrates the uncertainty in QALY results, and the spread of the points vertically demonstrates the uncertainty in the cost results. Nonetheless, the cloud of points falls within the northeast quadrant, indicating higher costs and better outcomes. An overview of all assumptions regarding the PSA parameters is presented in Appendix J – Probabilistic sensitivity analyses. The cost-effectiveness acceptability curve (CEAC) is presented in Figure 30.

Figure 29. Cost-effectiveness plane

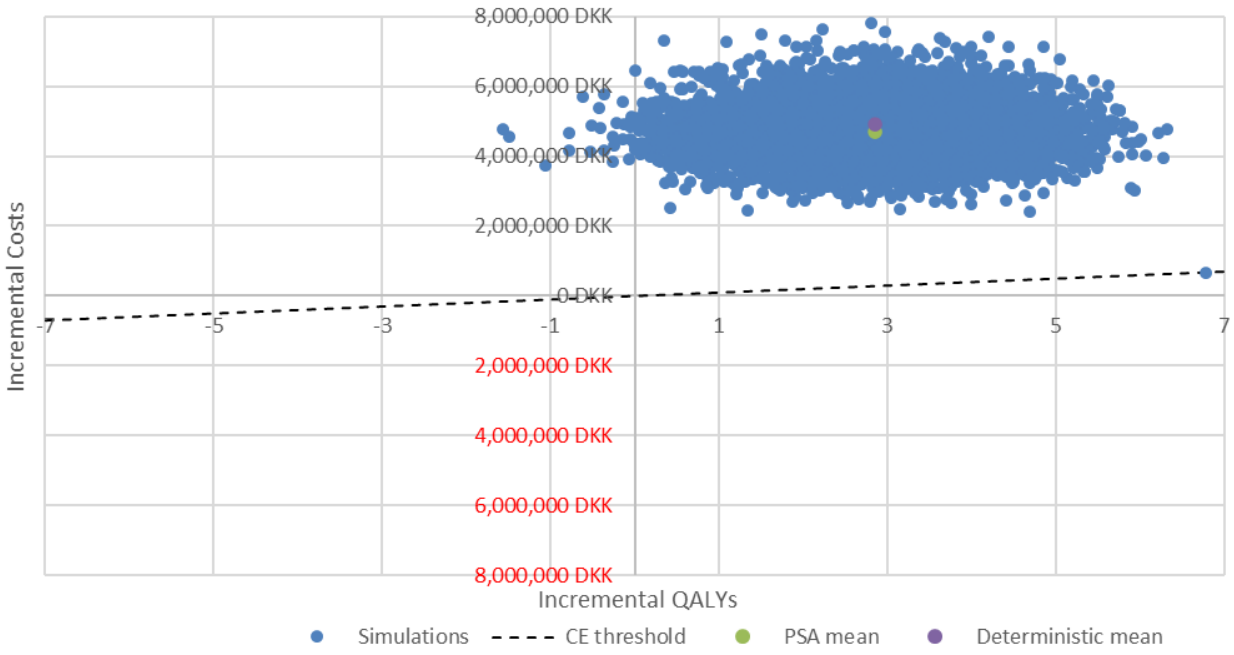
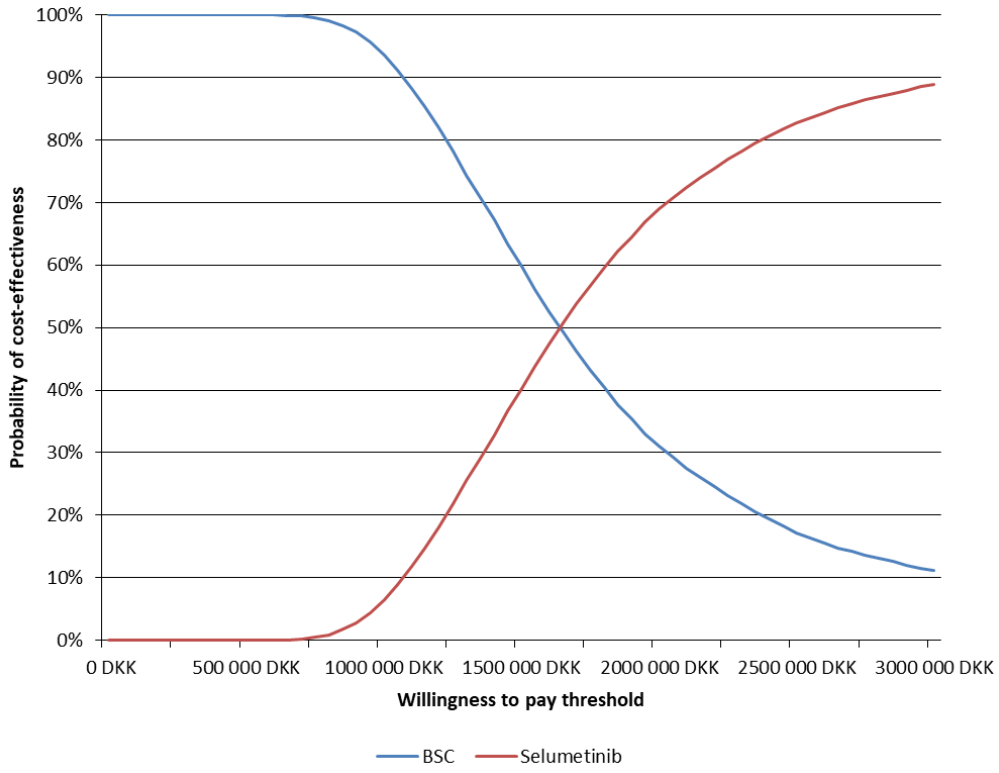


Figure 30. Cost-effectiveness acceptability curve (CEAC)



The CEAC indicates that at a willingness to pay of approximately 1,650,000 DKK/QALY, the probability of cost-effectiveness of the treatment with selumetinib is 50%. Further details concerning the distribution used for the parameters in the PSA are available in Appendix J – Probabilistic sensitivity analyses.

8.8 Managed Entry Agreement (MEA)

8.8.1 Motivation for managed entry agreement

A managed entry agreement (MEA) offers an alternative to the standard flat discount, a uniform discount applied to selumetinib that does not consider the value and outcomes associated with its use to treat symptomatic, inoperable PN in paediatric patients with NF1 in Denmark. From a clinical perspective, MEAs can be particularly viable when dealing with innovative treatments that offer significant potential benefits but are associated with uncertainties, e.g., by extrapolating the real-world effectiveness from the clinical trial efficacy data.

From an economic perspective, MEAs can provide a more flexible and risk-sharing approach to reimbursement, compared to a standardized flat discounted price. By linking reimbursement of a treatment to its performance, the MEA can help ensure that healthcare payers only pay for the actual value delivered by the treatment. This can lead to more efficient resource allocation, as funds are not wasted on ineffective treatments.

From a societal perspective, MEAs can help address concerns about the affordability and accessibility of innovative treatments. By allowing for more targeted pricing and reimbursement, MEAs can ensure that patients who stand to benefit the most from a treatment can access it, even if it has uncertain outcomes. This can lead to more equitable access to healthcare and better overall health outcomes for society.

In conclusion, adopting an MEA over a standardized flat discounted price can be a viable approach from a clinical, economic, and societal perspective. MEAs offer the potential for more efficient resource allocation, better risk-sharing

between stakeholders, and improved access to innovative treatments. However, it is important to consider the specific context and potential challenges associated with implementing an MEA, such as administrative complexity and the need for robust data collection and monitoring systems. The suggested MEA for selumetinib reflects these challenges.

[redacted]

[redacted]

8.8.5 Implementation in the health economic model

[redacted]

[redacted]

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9. Budget impact analysis

The budget impact of selumetinib is presented below in Table 48-Table 52. Prices are pharmacy purchasing price (PPP/AIP) as those described in Section 8.5. All costs relevant to the analysis have been included, namely the drug acquisition price of Koselugo® and the option to include a one-off cost for AEs if they are selected in the main model. Per patient costs from the first five years of the cost-effectiveness analysis were used to inform the budget impact analysis. The calculation employs an open cohort with patients entering each year, and the numbers of patients are based on the proportion described in Section 5.1.2. It is important to highlight that given the assumption on the BSC, the entirety of the cost is driven by selumetinib prices, therefore in the scenario where the pharmaceutical is not introduced, no costs would be included in the model. Hence the budget impact within this context is illustrative of the expenditures related to selumetinib in the first 5 years.

Number of patients

Table 48. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Selumetinib	25	27	29	31	33
BSC	0	0	0	0	0
Total number of patients	25	27	29	31	33

Table 49. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Selumetinib	0	0	0	0	0
BSC	25	27	29	31	33
Total number of patients	25	27	29	31	33

Expenditure per patient

Table 50. Costs per year - if the pharmaceutical is recommended

Costs category	Year 1		Year 2		Year 3		Year 4		Year 5	
	Selumetinib	BSC	Selumetinib	BSC	Selumetinib	BSC	Selumetinib	BSC	Selumetinib	BSC
Drug acquisition	23,768,654 DKK	0 DKK	21,920,072 DKK	0 DKK	23,377,998 DKK	0 DKK	21,331,801 DKK	0 DKK	21,717,224 DKK	0 DKK
AEs Cost	203,886 DKK	0 DKK	16,311 DKK	0 DKK	16,311 DKK	0 DKK	16,311 DKK	0 DKK	16,311 DKK	0 DKK
Total Cost	**23,972,540 DKK**		**21,936,383 DKK**		**23,394,309 DKK**		**21,348,112 DKK**		**21,733,535 DKK**	

Table 51. Costs per year - if the pharmaceutical is NOT recommended

Costs category	Year 1		Year 2		Year 3		Year 4		Year 5	
	Selumetinib	BSC	Selumetinib	BSC	Selumetinib	BSC	Selumetinib	BSC	Selumetinib	BSC
Drug acquisition	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
AEs cost	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
Total Cost	**0 DKK**		**0 DKK**		**0 DKK**		**0 DKK**		**0 DKK**	

Budget impact

Table 52. Expected budget impact of introducing the pharmaceutical at the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is introduced	23,972,540 DKK	21,936,383 DKK	23,394,309 DKK	21,348,112 DKK	21,733,535 DKK
Minus: **The pharmaceutical under consideration is NOT introduced**	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
Budget impact of the recommendation	**23,972,540 DKK**	**21,936,383 DKK**	**23,394,309 DKK**	**21,348,112 DKK**	**21,733,535 DKK**

10. Discussion on the submitted documentation

10.1 Summary of the submitted evidence

Selumetinib is developed to control and reduce the volume of PN and it is given in combination with BSC for patients with inoperable and symptomatic NF1 PN, for paediatric patients aged 3 or older. The pivotal trial SPRINT was used to source the efficacy and safety data for the health economic assessment of selumetinib in comparison to BSC, which was considered the most relevant comparator in the Danish clinical practice.
The SPRINT Phase 2 Stratum I is considered the most relevant study as it investigates 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. In the trial, a total of 50 paediatric patients with NF1 and symptomatic, inoperable PN were enrolled from August 2015 to August 2016 in this interventional, Phase 2, open label study conducted in four centres in the US.

10.2 Cost-effectiveness analysis

The objective of this analysis was to evaluate the cost-effectiveness of selumetinib compared to best supportive care in the treatment of paediatric patients with NF1 and symptomatic inoperable PN over a lifetime horizon from a Danish restricted societal perspective.

The key model inputs were treatment duration and progression-free survival, which were based on the clinical trial SPRINT. Utilities were derived from a vignette-based time-trade-off study. Costs and other relevant inputs were sourced from public sources and published literature.

Selumetinib was associated with higher costs and gains in quality adjusted life-years with the cost per additional QALY gained of DKK 1,728,474 over a lifetime horizon (100 years). The results of the analysis were sensitive, among other factors, to the time horizon, the discount rates, the inclusion of caregiver disutility and the choice of parametric model for time to discontinuation.

From a Danish restricted societal perspective, selumetinib in combination with best supportive care was estimated to lead to more QALYs gained at an increased cost compared to best supportive care alone for the treatment of paediatric patients with NF1 and symptomatic inoperable PN.

10.2.1 Strength of the analysis

A transparent, cost-effectiveness model was developed in Microsoft Excel and Microsoft Visual Basic for Applications. The model was adapted to a Danish setting according to the DMC's guidelines. A simplified area under the curve (AUC) approach was deemed the most appropriate structure for estimating the cost-effectiveness, since this approach reduces the number of assumptions required by alternative model structures due to the progressive natural history of NF1 PN, the disease heterogeneity, and the limited data availability.
The analysis framework captures the lifetime of patients and uses a 1 year cycle length.

Where possible, data were used from the SPRINT trial in the base-case analysis, which represents the target population for the treatment, and baseline characteristics such as age and BSA were adapted to represent the Danish patients. Additionally, the model includes health state utility weights derived from HRQoL data collected and adapted from the

SPRINT trial. Unit costs were taken from recognized national sources (where available). Extensive sensitivity analysis was performed, including univariate and probabilistic sensitivity analyses incorporating all model parameters.

10.3 Limitations

Nonetheless, this analysis has its own limitations. The number of patients in the SPRINT was low, while the progress free comparison is derived with a matching algorithm which might be subjected to some degree of uncertainties. Furthermore, data on NF1 patients, given the rarity of the disease, suffer from scarcity. Additionally, as a consequence of the limited availability of data and its heterogeneity, it was not possible to establish a robust association between target PN volume and HRQoL.

HRQoL were measured with PedsQL values. However, there are no appropriate algorithms to map PedsQL values to EQ-5D-5L index scores. Moreover, the HRQoL data from SPRINT were only available for patients treated with selumetinib for up to 3 years of follow-up and no alternative utility values have been reported for NF1 PN patients. Therefore, there were insufficient data to address the entire patient lifetime in a cost-effectiveness analysis of selumetinib compared to BSC. Instead, a vignette-based time-trade-off (TTO) study was performed, as described in Appendix K – HSUV related study, which might be subjected to uncertainties.
Furthermore, the addition of PFS health states to the BSC arm presents a challenge in properly determine the correct utility to assign for those patients who do not progress by clinical trial criterium, but are not on treatment and still suffer from the negative consequence of NF1 PN, resulting in a conservative estimate of the effect of selumetinib.

11. List of experts

Not applicable

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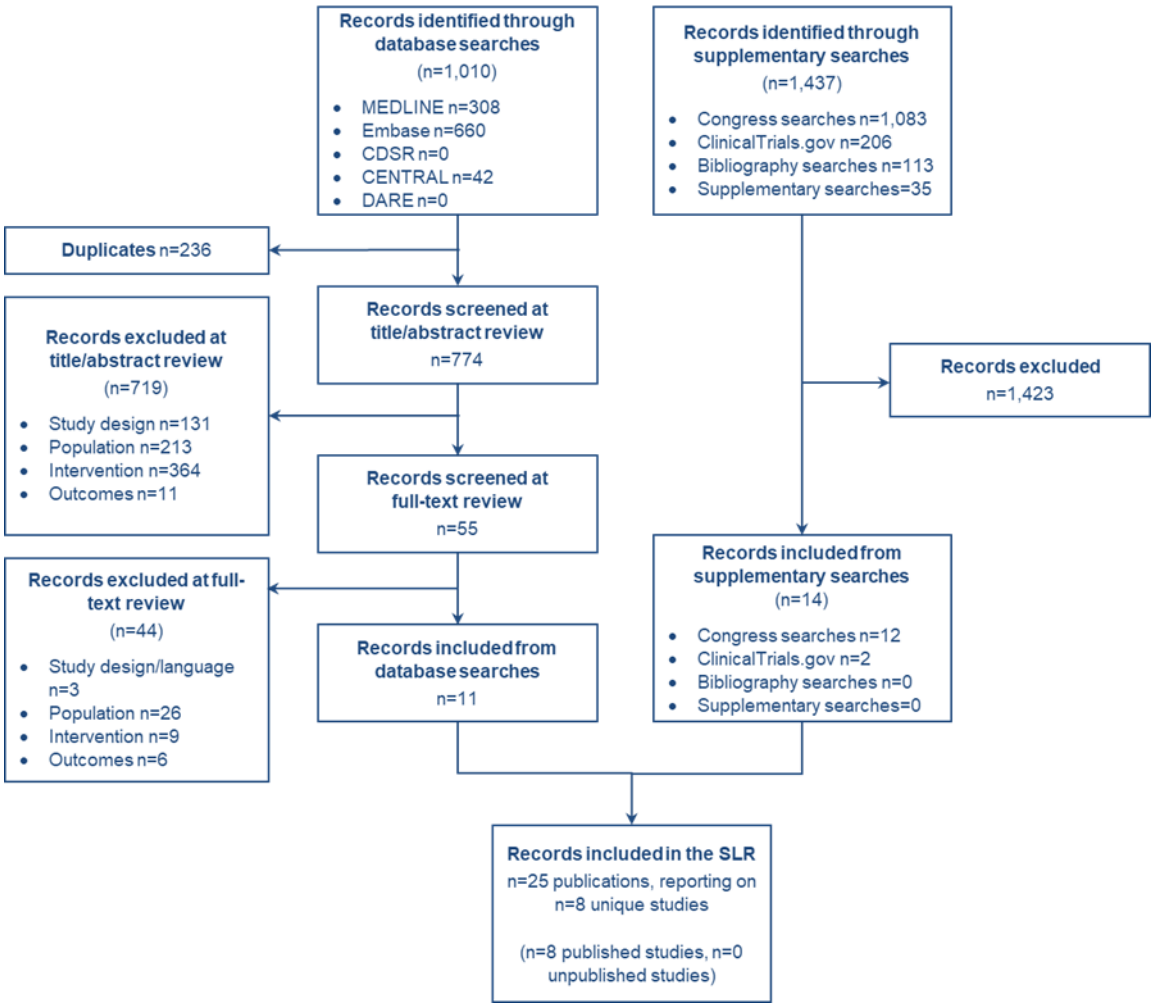
Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Objective of the literature search: The SLR aims to understand patient characteristics, treatment patterns, and health care resource use and costs among patients with diagnosed NF1 with PN and to identify evidence gaps in the above-mentioned areas.

Below in Figure 31 and Table 53 to Table 58 are reported the PRISMA diagram and the search strings used for the SLR.

Figure 31. 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.

Table 53. Search terms for MEDLINE, MEDLINE In-Process and Embase (searched via the Ovid SP platform, 07.09.22)

	#	Searches	Results
Disease area: NF1 PN	1	exp Neurofibromatosis 1/	10,517
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kf.	8,788
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kf.	9,393

	4	or/1-3	17,852
	5	neurofibroma/ or Neurofibroma, Plexiform/	4,609
	6	(plexiform neurofibroma$ or plexiform neuroma$).ti,ab,kf.	1,461
	7	or/5-6	5,312
Study design: RCTs	8	4 and 7	1,850
	9	randomized controlled trials as topic/	157,540
	10	randomized controlled trial/	576,388
	11	random allocation/	106,877
	12	double blind method/	172,946
	13	single blind method/	32,168
	14	clinical trial/	536,049
	15	controlled clinical trial/	95,017
	16	multicenter study/	325,243
	17	clinical trial, phase i.pt.	24,196
	18	clinical trial, phase ii.pt.	38,569
	19	clinical trial, phase iii.pt.	20,927
	20	clinical trial, phase iv.pt.	2,361
	21	controlled clinical trial.pt.	95,017
	22	randomized controlled trial.pt.	576,388
	23	multicenter study.pt.	325,243
	24	clinical trial.pt.	536,049
	25	exp clinical trials as topic/	376,826
	26	(clinical adj trial$).ti,ab,kf.	459,709
	27	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	191,230
	28	placebos/	35,922
	29	placebo$.ti,ab,kf.	239,931
	30	(allocat$ adj2 random$).ti,ab,kf.	41,473
	31	(Randomi?ed adj2 trial$).ti,ab,kf.	400,296
	32	rct.ti,ab,kf.	31,061
	33	or/9-32	1,960,248
Study design: Non-RCTs/observational studies	34	exp Epidemiologic studies/	3,005,295
	35	exp case control studies/	1,350,639
	36	exp Cohort Studies/	2,390,537
	37	Case control.ti,ab,kf.	147,616
	38	(cohort adj (study or studies)).ti,ab,kf.	289,334
	39	cohort analy$.ti,ab,kf.	11,530
	40	(follow up adj (study or studies)).ti,ab,kf.	56,215
	41	(observational adj (study or studies)).ti,ab,kf.	147,120
	42	Longitudinal$.ti,ab,kf.	324,508
	43	retrospective$.ti,ab,kf.	946,861
	44	Cross sectional.ti,ab,kf.	468,577
	45	Cross-sectional studies/	439,027

	46	exp Longitudinal Studies/	160,335
	47	exp Follow-Up Studies/	687,164
	48	exp Prospective Studies/	637,730
	49	exp Retrospective Studies/	1,055,892
	50	(Follow up adj (study or studies)).ti,ab,kf.	56,215
	51	(Prospective adj (study or studies)).ti,ab,kf.	200,268
	52	(evaluation adj (study or studies)).ti,ab,kf.	7,066
	53	(epidemiologic adj (study or studies)).ti,ab,kf.	28,636
	54	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kf.	8,145
	55	(Open-label adj (trial$ or stud$)).ti,ab,kf.	12,885
	56	Non-blinded stud$.ti,ab,kf.	139
	57	(chart adj3 review).ti,ab,kf.	48,175
	58	or/34-57	3,796,768
Exclusion Terms	59	exp animals/ not exp humans/	3,796,768
	60	(comment or editorial).pt.	5,042,506
	61	historical article/	1,402,101
	62	or/59-61	368,692
Combined	63	8 and (33 or 58)	6,738,326
	64	63 not 62	371
	65	limit 64 to yr="2021 -Current"	64

Database(s): Searches included Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, from 1946 to September 7th, 2022

Table 54. Search terms for Embase (searched via the Ovid SP platform, 09.07.22)

	#	Searches	Results
Disease area: NF1 PN	1	exp neurofibromatosis type 1/	4,913
	2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kw.	11,209
	3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kw.	14,059
	4	or/1-3	19,445
	5	neurofibroma/	7,040
	6	(plexiform neurofibroma$ or plexiform neuroma$).ti,ab,kw.	1,846
	7	or/5-6	7,764
	8	4 and 7	2,715
Study design: RCTs	9	"randomized controlled trial (topic)"/	233,885
	10	randomized controlled trial/	727,307
	11	clinical trial/	1,046,154
	12	exp "clinical trial (topic)"/	401,757
	13	controlled clinical trial/	468,234
	14	multicenter study/	335,966
	15	randomization/	95,013
	16	single blind procedure/	47,455
	17	double blind procedure/	198,823
	18	crossover procedure/	71,382

	19	placebo/	385,648
	20	phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	201,925
	21	(clinical adj trial$).ti,ab,kw.	640,333
	22	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kw.	267,768
	23	placebo$.ti,ab,kw.	349,119
	24	(allocat$ adj2 random$).ti,ab,kw.	51,154
	25	(Randomi?ed adj2 trial$).ti,ab,kw.	528,496
	26	rct.ti,ab,kw.	50,424
	27	or/9-26	2,760,754
Study design: Non-RCTs/observational studies	28	exp epidemiology/	4,135,230
	29	exp case control study/	210,629
	30	exp cohort analysis/	890,154
	31	Case control.ti,ab,kw.	192,252
	32	(cohort adj (study or studies)).ti,ab,kw.	410,937
	33	cohort analy$.ti,ab,kw.	17,423
	34	(Follow up adj (study or studies)).ti,ab,kw.	70,291
	35	(observational adj (study or studies)).ti,ab,kw.	225,449
	36	Longitudinal$.ti,ab,kw.	437,899
	37	retrospective$.ti,ab,kw.	1,564,813
	38	Cross sectional.ti,ab,kw.	607,392
	39	Cross-sectional study/	502,192
	40	exp Longitudinal study/	177,850
	41	exp follow up/	1,889,346
	42	exp retrospective study/	1,301,195
	43	exp observational study/	286,378
	44	(Prospective adj (study or studies)).ti,ab,kw.	299,751
	45	(evaluation adj (study or studies)).ti,ab,kw.	8,631
	46	(epidemiologic adj (study or studies)).ti,ab,kw.	34,378
	47	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kw.	16,819
	48	(Open-label adj (trial$ or stud$)).ti,ab,kw.	22,914
	49	Non-blinded stud$.ti,ab,kw.	212
	50	(chart adj3 review).ti,ab,kw.	101,636
	51	or/28-50	7,640,903
Exclusion terms	52	("conference abstract" or "conference review").pt.	4,536,774
	53	limit 52 to yr="1974-2018"	4,126,125
	54	exp animals/ not exp humans/	4,993,925
	55	(comment or editorial).pt.	737,789
	56	historical article/	1
	57	or/52-56	9,464,443
Combined	58	8 and (27 or 51)	974
	59	58 not 57	798

	60	limit 59 to yr="2021 -Current"	186

Database: Embase from 1974 to September 7th, 2022

Table 55. Search terms used in CDSR and CENTRAL (searched simultaneously via the Cochrane Library Wiley online platform on 7th September 2022)

#	Searches	Results
1	[mh “neurofibromatosis 1”]	65
2	("1" or i or peripheral or von Recklinghausen) near/2 neurofibroma*:ti,ab,kw	138
3	(NF1 or NFI or NF-1 or NF-I):ti,ab,kw	276
4	(or #1-#3)	309
5	[mh ^“neurofibroma”] OR [mh ^“neurofibroma, Plexiform”]	51
6	(plexiform neurofibroma* or plexiform neuroma*):ti,ab,kw	21
7	(or #5-#6)	66
8	#4 and #7	13
9	#8 in Trials	65
10	#8 in Cochrane Reviews, Cochrane Protocols	138

Database: For both CDSR and CENTRAL, the most recent issue searched was Issue 1 of 12, January 2021.

Table 56. 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

Table 57. 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
ASCO Annual Meeting: 2021	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: Meeting: ASCO Virtual Scientific Program Date: 2021 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"	41 screened; 0 included
ASCO Annual Meeting: 2022	https://meetinglibrary.asco.org/	Using the "Advanced Search" option, the following filters were applied: Meeting: ASCO Virtual Scientific Program Date: 2022 The following string was then searched for using the Advanced Search function:	43 screened; 1 included

		(Keywords:"neurofibrom*" OR Keywords:"NF-1" OR Keywords:"NF1" OR Keywords:"plexiform" OR Keywords:"von Recklinghausen"	
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&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
ASPHO 2021	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM21&ssoOverride=OFF&USERPID=PUBLIC	The 2021 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. "NF-1" 3. NF1 4. Plexiform 5. Von Recklinghausen's	1 screened; 0 included
ASPHO 2022	https://aspho.planion.com/Web.User/AbsSearch?ACCOUNT=ASPHO&CONF=AM22&ssoOverride=OFF&USERPID=PUBLIC	The 2022 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. "NF-1" 3. NF1 4. Plexiform 5. Von Recklinghausen's	2 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
Children's Tumor Foundation NF Conference: 2021	https://www.ctf.org/images/uploads/documents/21_NFVirtualConference.pdf	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	51 screened; 9 included
Children's Tumor Foundation NF Conference: 2022	https//drive.google.com/file/d/1KTZqH5lOxSROSwP-AAv4v5NHdOVcBvlC/view	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	57 screened; 8 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
ESMO Congress 2021	https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress	The 2021 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. "NF-1" 3. NF1	2 screened; 0 included

		4. Plexiform 5. Von Recklinghausen's	
ESMO Congress 2022	https://www.esmo.org/meetings/past-meetings/esmo-congress-2022	The 2022 conference website was searched in turn for the following terms: 1. Neurofibrom* 2. "NF-1" 3. NF1 4. Plexiform 5. Von Recklinghausen's	2 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
ISPNO: 2022[b]	FULL ISPNO 2022 ABSTRACTS PDF | Neuro-Oncology | Oxford Academic (oup.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	42 screened; 1 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* Von Recklinghausen's	5 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 Neurofibrom* Von Recklinghausen's	0 screened; 0 included
ISPOR Annual European and International Meetings 2021 and 2022 (International Meeting only)	https://www.ispor.org/heor-resources/presentations-database/search	The following terms were searched in the "Keyword" field: 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.

Table 58. Search terms used for ClinicalTrials.gov (searched on 14th Septmeber 2022)

#	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	219 screened; 11 included

Inclusion and exclusion criteria used for for the SLR are presented in Table 59.

Table 59. 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 DMC 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 DMC decision problem
Comparator	Any (including established clinical management) or none	N/A	Aligned to the DMC 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 PN volume change Growth rate of PN Effect on physical functioning Effect on pain • Safety outcomes, including but not limited to:	Studies not presenting relevant outcomes (See Inclusion criteria)	These outcomes encompass the clinical outcomes specified as relevant in the DMC decision problem for this submission

	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 • 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	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
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

Details of the eight published studies meeting the pre-defined inclusion criteria of the SLR are presented in Table 60. References to the published study are listed in Table 61.

Table 60. Studies meeting the pre-defined inclusion criteria of the SLR

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)
Al-Mulla 2022	Interventional retrospective case series	Al-Mulla 2022	Paediatric patients with NF1 and inoperable PN	Selumetinib	N/A	Safety, tumour response to selumetinib, resolution of pain, improved functionality
Baldo 2020	Interventional prospective case-series	Baldo 2020	Paediatric patients with NF1 and inoperable PN	Selumetinib	N/A	Safety, tumour response
Baldo 2021	Case series	Baldo 2021	Paediatric patients with NF1 and PN	Selumetinib	N/A	Incidence of peripheral oedema and hair colour change
Coltin 2022	Interventional retrospective case series	Coltin 2022	Paediatric patients with NF1 and symptomatic PN	Selumetinib	N/A	Safety, symptomatic improvement, tumour response
Coyne 2019	Phase II, on-interventional study (single-arm trial)	NCT02407405	Adult (≥18 years) patients with NF1, inoperable PN and ≥1 PN-related morbidity	Selumetinib	N/A	Change in PN volume, partial RR, complete RR, safety, pharmacodynamics, pain
Dombi 2016	Interventional, open-label study	NCT01362803 SPRINT: Phase I	Children with NF-1 and inoperable PN	Selumetinib	N/A	PR, time to best response, safety
Espirito Santo 2020	Case-series	Espirito Santo 2020	Genetically confirmed NF1 patients (aged 3–19) with inoperable PN associated with	Selumetinib	N/A	Clinical improvement, PN size, clinical/radiological progression, safety

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)
			significant or potentially significant morbidity			
Fisher 2021	Phase II, open-label study	NF105-CABO (NCT02101736)	Patients aged 16 years or older with NF1 and progressive or symptomatic, inoperable PN; Patients aged 3–15 also included in the trial, however results are not yet published for this patient group	Cabozantinib	N/A	Rate of patients achieving PR, safety, PROs, QoL, pharmacokinetics, levels of circulating endothelial cells and cytokines
Gross 2020	Interventional, open-label study	NCT01362803 SPRINT: Phase II, stratum 1	Patients with NF1 with inoperable PN (aged 2–18 years)	Selumetinib	N/A	ORR, BOR, PR, PFS, functional outcomes, HRQoL, GIC, safety
Gross 2022	Interventional study	SPRINT: Phase II, stratum 2	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, patient-reported outcomes, observer-reported outcomes, safety
Gupta 2003	Interventional, open-label, Phase I trial	Gupta 2003	Patients aged >5 years, with NF1 and disabling, inoperable PN	Thalidomide	N/A	Tumour response, symptomatic improvement, safety
Hounjet 2020	Case-report	Hounjet 2020	Children with life threatening,	Trametinib	N/A	Safety, clinical benefit

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)
			extensive, symptomatic PN			
Hu 2022	Interventional, open-label, Phase I dose escalation and Phase II dose-expansion trial	NCT04954001	Adults with NF1 and PN that was not completely resectable or not suitable for surgery	FCN-159	N/A	Safety, tumour response
Kim 2013	Interventional, single-arm trial	Kim 2013	Children between 3 and 18 years of age with NF1 and inoperable PN	Sorafenib	N/A	Toxicity, response, pharmacokinetics, pharmacodynamics, QoL, medication adherence
Kudek 2019	Interventional, case-report	Kudek 2019	Paediatric NF1 patients with inoperable PN	Selumetinib or trametinib	N/A	Disease progression, safety
Moertel 2018	Phase I/IIa non-randomised interventional study	NCT02124772	Patients with NF-1 with unresectable PN (one month to ≤18 years age)	Trametinib	N/A	TRAEs, partial response
Moertel 2021	Phase IIb, open-label study	ReNeu	Adult/paediatric patients with an inoperable NF1-PN causing significant morbidity	Mirdametinib	N/A	Tumour response, DOR, safety
Passos 2020	Interventional case-study	Passos 2020	14-year-old boy with NF1 and PN, undergone partial resection	Selumetinib	N/A	Lansky Performance Scale, toxicities
Passos 2021	Single-arm interventional study	Passos 2021	Adult/paediatric patients with symptomatic/ inoperable NF1-PN	Selumetinib	N/A	Tumour response, PROs, safety

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)
Reddy 2021	Phase II, open-label study	Reddy 2021	Adult patients (≥18 years) with NF1 and progressive PN or PN causing significant morbidity	Binimetinib	N/A	Tumour response, safety
Ronsley 2021	Interventional retrospective case series	Ronsley 2022	Patients <20 years of age with severe PN	Trametinib	N/A	Tumour response, functional changes, safety
Sadat Kiaei 2022	Phase II, open-label study	TRAM-01	Patients ≤25 years of age with NF1 and PN (Group 2[f])	Trametinib	N/A	Tumour response, neuropsychological evaluation, QoL, safety
Salvador 2018	Single-arm interventional study	Salvador 2018	Patients with symptomatic unresectable NF1 and PN	Trametinib	N/A	Number of patients with tumour progression or tumour volume reduction
Toledano 2021	Case series	Toledano 2021	Paediatric patients with NF1 and orbital PN	Trametinib	N/A	Tumour response, visual function, safety
Trippet 2022	Phase I/II, open-label study	iMATRIX-cobi	Patients with histologically/ cytologically confirmed tumours with known/expected MAPK pathway involvement (including NF1-PN)	Cobimetinib	N/A	Response, pharmacokinetics, overall survival, safety
Vaassen 2019	Case study	Vaassen 2019	11-year-old girl with NF1 and inoperable PN	Trametinib	N/A	MRI volumetric response, side effects
Vaassen 2022	Case series	Vaassen 2022	Paediatric patients with NF1 and PN	Selumetinib or trametinib	N/A	Response, safety

Primary study reference	Study type	Study name	Population	Intervention	Comparator	Results reported (list)
Vassallo 2019	Interventional case-study	Vassallo 2019	Four-year-old boy with NF1 and a large PN, considered inoperable with no other treatment options available	Trametinib	N/A	PN size, safety
Venialgo 2022	Medical record review	Venialgo 2022	Paediatric patients with NF1 and symptomatic and unresectable PN	Trametinib	N/A	Tumour response, safety
Wagner 2022	Phase II clinical study	NCT00030264	Children or young adults (<25 years) with progressive, debilitating, severely disfiguring or life-threatening PN which is unresectable	Combination chemotherapy: methotrexate and vinblastine	N/A	Time to disease progression, all-cause mortality, functional improvements, safety
Wang 2021	Case series	Wang 2021	Paediatric patients ≤6 years with symptomatic, inoperable NF1-PN	Selumetinib	N/A	Tumour response, symptom improvement, patient-reported outcome, safety
Weiss 2021	Phase II clinical study	NCT02096471	Patients aged ≥16 years with NF1 and PN	Mirdametinib	N/A	Tumour response, patient-reported outcomes, safety, pharmacokinetics

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. aStudies are pooled analyses reporting data on both SPRINT Phase II, stratum 1 and NCT02407405, bStudy is the ClinicalTrials.gov record associated with SPRINT (Phase I, Phase II Stratum 1, and Phase II Stratum 2), cStudy is a pooled analysis reporting data on SPRINT trials (Phase I, Phase II Stratum 1, and Phase II Stratum 2), dStudy is a pooled analysis reporting data on SPRINT Phase II trials (Phase II Stratum 1, and Phase II Stratum 2), eIncludes patients enrolled on NCT03962543 (Mirdametinib; reported in Moertel 2021), NCT02096471 (Mirdametinib; reported in Weiss 2021), NCT02407405 (Selumetinib; reported in Coyne 2019, 2020a, 2020b and Martin 2019), and NCT02124772 (Trametinib; reported in Moertel 2018),

fThere were three other eligible groups: Group 1, NF1 with progressing/refractory LGG; Group 3, progressing/refractory LGG with KIAA1549-BRAF fusion.; Group 4, progressing/refractory glioma with activation of the MAPK/ERK pathway who do not meet criteria for other study groups gStudy reports long-term (over 24 cycles) medication adherence in subjects enrolled on Phase II, Stratum 1 and Stratum 2 of SPRINT (data not extracted in current report)

Table 61. List of included studies in the SLR

#	Study name	Citation
Published studies		
1	Al-Mulla 2022	Al-Mulla, A. Neurofibromatosis Type 1 Patients with Plexiform Neurofibromas Treated with Selumetinib. Pediatric Blood and Cancer. 2022. 69(SUPPL 2):S37.
2	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.
3	Baldo 2021	Baldo F, Magnolato A, Barbi E, et al. Selumetinib side effects in children treated for plexiform neurofibromas: first case reports of peripheral edema and hair color change. BMC Pediatr. 2021 Feb 6;21(1):67. doi: 10.1186/s12887-021-02530-5
4	Coltin 2022	Coltin H, Perreault S, Larouche V, et al. Selumetinib for symptomatic, inoperable plexiform neurofibromas in children with neurofibromatosis type 1: A national real-world case series. Pediatr Blood Cancer. 2022 Aug;69(8):e29633.
5	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.
6	Gupta 2003	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.
7	Hounjet 2020	Hounjet C, Ronsley R, Cheng S, et al. NFB-12. Trametinib Therapy for Pediatric Patients With Refractory Low Grade Glioma Or Extensive Symptomatic Plexiform Neurofibroma. Neuro-Oncology 2020;22:iii420 - iii420.
8	iMATRIX-cobi	Trippett T, Toledano H, Campbell Hewson Q, et al. Cobimetinib in Pediatric and Young Adult Patients with Relapsed or Refractory Solid Tumors (iMATRIX-cobi): A Multicenter, Phase I/II Study. Target Oncol. 2022 May;17(3):283-293.
9	Kim 2013	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.
10	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.
11	NCT02096471	Weiss BD, Wolters PL, Plotkin SR, et al. NF106: A Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK Inhibitor Mirdametinib (PD-0325901) in Adolescents and Adults With NF1-Related Plexiform Neurofibromas. J Clin Oncol. 2021 Mar 1;39(7):797-806.
12	NCT02124772	CT.gov. Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations, 2021.
13		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.
14		Moertel C. Trametinib in Pediatric Patients with Neurofibromatosis Type 1 (NF-1)–Associated Plexiform Neurofibroma: A Phase I/IIa Study. Joint Global Neurofibromatosis Conference 2018, 2018.
15	NCT02407405	CT.gov. MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas, 2020.

#	Study name	Citation
16		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.
17		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.
18		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.
19		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.
20		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]
21		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]
22		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]
23		Tibery C, Ong, MJ, Comis LE et al. Incidence and Management of Peripheral Edema (PerE) in a Phase II Study of the MEK Inhibitor (MEKi) Selumetinib in Adult Patients with Neurofibromatosis Type 1 (NF1) with Inoperable, Symptomatic Plexiform Neurofibromas (PN). Presented at 2022 NF Virtual Conference. June 18-21, 2022.
24	NCT00030264	CT.gov. Combination Chemotherapy in Treating Patients With Neurofibromatosis and Progressive Plexiform Neurofibromas, 2018.
25		Wagner K, Kotch C, Harris Broad J, et al. Vinblastine and methotrexate for severe, progressive plexiform neurofibroma: a phase 2 clinical trial. Presented at 2022 NF Virtual Conference. June 18-21, 2022.
26	NCT04954001	CT.gov. Study to Evaluate the Safety, Tolerability, PK Characteristics and Anti-tumor Activity of FCN-159 in Adult and Pediatric Participants With Neurofibromatosis Type 1, 2022.
27		Hu X, Zeng K, Zhongyuan X, et al. A multicenter, open-label, single-arm, phase 1 dose-escalation study to evaluate the safety, tolerability, and anti-tumor activity of FCN-159 in adults with neurofibromatosis type 1. Journal of Clinical Oncology 2022; 40 (16_suppl): 3011-3011.
28	NF105-CABO	CT.gov. Cabozantinib for Plexiform Neurofibromas (PN) in Subjects With NF1 in Children and Adults, 2021.
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.
30		Fisher MJ. A Neurofibromatosis Clinical Trials Consortium (NFCTC) Phase II Study of Cabozantinib (XL184) for Neurofibromatosis Type 1 (NF1) Associated Plexiform Neurofibromas. Joint Global Neurofibromatosis Conference 2018.

#	Study name	Citation
31		Blakeley J, Dombi E, Clapp W et al. Cabozantinib (XL184) for the Treatment of Neurofibromatosis Type 1-Associated Plexiform Neurofibromas (NF1-PN) in Children: A Neurofibromatosis Clinical Trials Consortium (NFCTC) Phase 2 Trial. Presented at 2022 NF Virtual Conference; June 18-21, 2022.
32	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.
33	Passos 2021	Passos J, Espirito Santo V, Abecasis N et al. Selumetinib for plexiform neurofibroma (PN) in neurofibromatosis type 1 (NF1): clinical experience from a single centre. Presented at 2021 NF Virtual Conference; June 14-16, 2021.
34	Reddy 2021	Reddy AT, Fisher MJ, Dombi E et al. Binimetinib leads to radiographic response in adults with neurofibromatosis type 1 associated plexiform neurofibromatosis: a report from the NFCTC and PNOC. Presented at 2021 NF Virtual Conference; June 14-16, 2021.
35	ReNeu	Moertel C, Babovic-Vuksanovic D, Gershon T. et al. ReNeu: Phase 2B trial of mirdametinib, a MEK1/2 inhibitor, in patients with NF1-associated plexiform neurofibroma causing significant morbidity. Presented at 2021 NF Virtual Conference; June 14-16, 2021b.
36		CT.gov. MEK Inhibitor Mirdametinib (PD-0325901) in Patients With Neurofibromatosis Type 1 Associated Plexiform Neurofibromas, 2022.
37	Ronsley 2021	Ronsley R, Hounjet CD, Cheng S, et al. Trametinib therapy for children with neurofibromatosis type 1 and life-threatening plexiform neurofibroma or treatment-refractory low-grade glioma. Cancer Med. 2021 Jun;10(11):3556-3564.
38	Salvador 2018	Salvador IM-S, Federico Ramos. Clinical and Radiological Efficacy Of Trametinib In Plexiform Neurofibromas In Patients With Neurofibromatosis Type 1. Joint Global Neurofibromatosis Conference 2018, 2018.
39	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.
40		CT.gov. AZD6244 Hydrogen Sulfate for Children With Nervous System Tumors, 2021.[b]
41		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]
42		Baldwin A, Dombi E, Fischer MJ, et al. Occurrence of Fractures in Children with Neurofibromatosis Type 1 on the MEK Inhibitor Selumetinib for Inoperable Plexiform Neurofibroma. Presented at 2021 NF Virtual Conference; June 14-16, 2021. [Also reports data for Phase II patients (Stratum 1 and 2)]
43		Gross AM, Baldwin A, Brofferio A, et al. Incidence of Ocular and Cardiac Adverse Events in Children with Neurofibromatosis Type 1 on a Phase 1/2 Study of Selumetinib for Inoperable Plexiform Neurofibromas. Presented at 2021 NF Virtual Conference; June 14-16, 2021b. [Also reports data for Phase II patients (Stratum 1 and 2)]
44		Gross AM, Baldwin A, Dombi E, et al. Long-Term Safety and Efficacy of Selumetinib in Children with Neurofibromatosis Type 1 on a Phase 1 Study for Inoperable Plexiform Neurofibromas. Presented at 2021 NF Virtual Conference; June 14-16, 2021.
45	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.

#	Study name	Citation
46		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.
47		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.
48		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.
49		Gross AM, Wolters PL, Dombi E, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. New England Journal of Medicine 2020;382:1430-1442.
50		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.
51		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.
52		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]
53		Gross AM, Wolters PL, Baldwin A, et al. Long-Term Safety and Efficacy of Selumetinib in Children with Neurofibromatosis Type 1 on a Phase 2 Study for Inoperable Plexiform Neurofibromas. Presented at 2021 NF Virtual Conference. June 14-16, 2021c.
54		Christensen JA, Gross AM, Dombi E, et al. Longitudinal Assessment of Hearing in Children with Neurofibromatosis Type 1 (NF1) and Facial/Head Plexiform Neurofibromas on the Phase 2 Selumetinib SPRINT Trial. Presented at 2021 NF Virtual Conference; June 14-16, 2021. [Also reports data for Stratum 2 patients]
55		Ibeku A, Dombi. E, Baldwin A, et al. Progression of Scoliosis in Children with Neurofibromatosis Type 1 on a Clinical Trial of Selumetinib for Inoperable Plexiform Neurofibroma. Presented at 2022 NF Virtual Conference; June 18-21, 2022. [Also reports data for Stratum 2 patients]
56		Wolters PL, Gross A, Martin S, et al. Prospective Patient-Reported Outcome (PRO) Measures Document Long-Term 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 (AZD6244, ARRY-142886). Presented at 2022 NF Virtual Conference. June 18-21, 2022.
57		Rhodes A, Wolters P, Baldwin A et al. Long Term Medication Adherence in Children and Adolescents with Neurofibromatosis Type 1 (NF1) on the SPRINT Trial for Selumetinib. Presented at 2022 NF Virtual Conference. June 18-21, 2022. [Also reports data for Stratum 2 patients]
58	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.

#	Study name	Citation
59		Glassberg B. Selumetinib in Children with Clinically Asymptomatic Inoperable Neurofibromatosis Type 1 Related Plexiform Neurofibromas. Children's Tumor Foundation NF Conference 2020, 2020.
60		Gross AM. Selumetinib in Children with Neurofibromatosis Type 1 and Asymptomatic Inoperable Plexiform Neurofibroma At Risk for Developing Tumor-Related Morbidity. Neuro Oncol. 2022 Apr 25:noac109. doi: 10.1093/neuonc/noac109
61	Toledano 2021	Toledano H, Dotan G, Friedland R, et al. Trametinib for orbital plexiform neurofibromas in young children with neurofibromatosis type 1. Childs Nerv Syst. 2021 Jun;37(6):1909-1915.
62	TRAM-01 (NCT03363217)	Sadat Kiaei D, Larouche V, Decarie J-C, et al. NFB-08. TRAM-01: A Phase 2 study of trametinib for pediatric patients with neurofibromatosis type 1 and plexiform neurofibromas. Neuro-Oncology 2022; 24 (suppl 1); i129
63		Perreault S, Larouche V, Tabori U, et al. A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the MAPK/ERK pathway: TRAM-01. BMC Cancer. 2019 Dec 27;19(1):1250.
64		Lalancette E, Cantin E, Routhier M-E, et al. Impact of Trametinib on the Neuropsychological Profile of NF1 Patients. Presented at 2022 NF Virtual Conference. June 18-21, 2022.
65	Vaassen 2019	Pia Vaassen MTR. Trametinib Induces Neurofibroma Shrinkage and Enables Surgery. Children's Tumor Foundation NF Conference 2019, 2019.
66	Vaassen 2022	Vaassen P, Dürr NR, Rosenbaum T. Treatment of Plexiform Neurofibromas with MEK Inhibitors: First Results with a New Therapeutic Option. Neuropediatrics. 2022 Feb;53(1):52-60. doi: 10.1055/s-0041-1740549. Epub 2021 Dec 14.
67	Vassallo 2019	Vassallo G. Gross Haematuria in a Child on MEK inhibitors. Children's Tumor Foundation NF Conference 2019, 2019.
68	Venialgo 2022	Venialgo G. Trametinib for paediatric NF1 patients with symptomatic plexiform neurofibroma with non surgical treatment option: real-world clinical experience. Presented at 2022 NF Virtual Conference. June 18-21, 2022.
69	Walsh 2021	Walsh KS, Wolters PL, Widemann BC et al. Impact of MEK Inhibitor Therapy on Neurocognitive Functioning in NF1. Neurol Genet Oct 2021, 7 (5) e616
70	Wang 2021	Wang Z. Selumetinib for plexiform neurofibromas (PN) in neurofibromatosis Type 1 (NF1): real-world clinical experiences in younger children. Presented at 2021 NF Virtual Conference. June 14-16.
Unpublished study		
71	NCT04924608	CT.gov. Efficacy and Safety of Selumetinib in Adults With NF1 Who Have Symptomatic, Inoperable Plexiform Neurofibromas
72	NCT05101148	CT.gov. Phase I Study to Assess the Effect of Food on the PK and Gastrointestinal Toxicity of Selumetinib in Adolescent Children With Neurofibromatosis Type 1 Related Plexiform Neurofibromas
73	NCT05331105	CT.gov. HL-085 in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas
74	EudraCT2020-05608-20	CT.gov. A Phase I/II, Single-Arm, Open label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 Years with Neurofibromatosis type 1

Table 62 shows the list of studies excluded in the clinical SLR at full-text review stage, and reasoning for exclusion.

Table 62. 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 refractory tumor and activation of the MAPK/ERK pathway: TRAM-01. BMC Cancer 2019;19 (1) (no pagination).	Irrelevant population

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	No relevant outcomes reported

	neurofibromas. Journal of Clinical Oncology 2006;24:507-516.	
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

Appendix B – Main characteristics of included studies

Below in Table 63 are reported the main characteristics of the most relevant study, which was identified in the SLR, SPRTINT Phase 2 Stratum I. The SLR identified eight studies meeting the pre-defined inclusion criteria. However, as mentioned in Section 6.2, SPRINT was deemed the most relevant.

Table 63. SPRINT Phase 2 Stratum I Main characteristics

Trial name: SPRINT Phase 2 Stratum I	NCT number: NCT01362803
Objective	Phase 2 of the SPRINT trial was a multicentre, open label study designed to evaluate the response rate to and clinical benefit of selumetinib treatment
Publications – title, author, journal, year	Gross, A.M., 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.
Study type and design	Phase 2, multicentre, open label study
Sample size (n)	50 selumetinib (patients aged 2–18 with NF1 and symptomatic, inoperable PN)

Main inclusion criteria

1. Age Phase 2: geater than 2 years of age and less than or equal to 18 years of age. BSA greater than or equal to 0.55 m(2), and able to swallow whole capsules.
2. Diagnosis: Patients with NF1 and inoperable PN, defined as PN that cannot be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN. The PN had to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, paraspinal lesions that can cause myelopathy brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Patients will be enrolled into stratum 1 based on PN related morbidity. Histiologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected.
   A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with connection between the levels or extending laterally along the nerve. In addition to PN, all study subjects must have either positive genetic testing for NF1 or have at least one other diagnostic criterion for NF1 listed below: (NIH Consensus conference):
   - Six or more café-au-lait macules (greater than or equal to 0.5cm in prepubertal subjects or greater than or equal to 1.5 cm in post pubertal subjects)
   - Freckling in axilla or groin
   - Optic glioma
   - Two or more Lisch nodules
   - A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
   - A first-degree relative with NF1
3. Measurable disease: Patients must have at least one measurable PN, defined as a lesion of at least 3 cm measured in one dimension. Patients who underwent surgery for resection of a PN are eligible provided the PN was incompletely resected and is measurable.
   Phase 2: Measurability and suitability for volumetric MRI analysis of the target PN must be confirmed with the NCI POB prior to enrolling a patient. The target PN will be defined as the clinically most relevant PN, which has to be amenable to volumetric MRI analysis. PN will be classified as typical PN versus nodular PN versus solitary nodular PN prior to enrollment
4. Prior Therapy: Patients with NF1 will only be eligible if complete tumor resection is not considered to be feasible without substantial risk or morbidity.
   - Since there is no standard effective chemotherapy for patients with NF1 and PN, patients may be treated on this trial without having received prior medical therapy directed at their PN.
   - Since selumetinib is not expected to cause substantial myelosuppression, there will be no limit to number of prior myelosuppressive regimen for PN or other tumor manifestations associated with NF1 such as optic glioma.
   - Patients who have received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorafenib, imatinib or other targeted therapies are eligible for enrollment. At least 4 weeks must

have elapsed since receiving medical therapy directed at the PN. Patients who received prior medical therapy for their PN must have recovered from the acute toxic effects of all prior therapy to less than or equal to grade 1 before entering this study.

- Growth factors that support platelet or white cell number or function must not have been administered within 7 days prior to enrollment.
- At least 6 weeks must have elapsed prior to enrollment since the patient received any prior radiation therapy.
- At least 4 weeks must have elapsed since any surgeries, with evidence of good wound healing.

5. Performance status: Patients greater than or equal to 16 years of age must have a Karnofsky performance level of greater than or equal to 70%, and children < 16 years old must have a Lansky performance of greater than or equal to 70%. Patients who are wheelchair bound because of paralysis secondary to a plexiform neurofibroma should be considered ambulatory when they are up in their wheelchair. Similarly, patients with limited mobility secondary to need for mechanical support (such as an airway PN requiring tracheostomy or CPAP) will also be considered ambulatory for the purpose of the study.
6. Hematologic Function: Patients must have an absolute neutrophil count greater than or equal to 1500/(micro)l, hemoglobin greater than or equal to 9g/dl, and platelet greater than or equal to 100,000/(micro)l.
7. Hepatic Function: Patients must have bilirubin within 1.5 times the upper limit of normal for age, with the exception of Gilbert syndrome, and AST/ ALT within less than or equal to 3 times the upper limit of normal.
8. Renal Function: Patients must have a creatinine clearance or radioisotope GFR greater than or equal to 60ml/min/1.73 m(2) or a normal serum creatinine based on age described below.

Age (years)/Maximum Serum Creatinine(mg/dL):

Age less than or equal to 5/Maximum Serum Creatinine 0.8 mg/dL

Age greater than 5 to less than or equal to 10/ Maximum Serum Creatinine 1.0 mg/dL

Age greater than 10 to less than or equal to 15/ Maximum Serum Creatinine 1.2 mg/dL

Age greater than 15/ Maximum Serum Creatinine 1.5 mg/dL

9. Cardiac Function: Normal ejection fraction (ECHO or cardiac MRI) greater than or equal to 53% (or the institutional normal; if a range is given then the upper value of the range will be used); QTcF less than or equal to 450 msec.
10. Adequate Blood Pressure defined as:

A blood pressure (BP) less than or equal to the 95th percentile for age, height, and gender. Adequate blood pressure can be achieved using medication for treatment of hypertension.

11. Informed Consent: Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent from all patients or their legal guardians (if the patient is <18 years old). When appropriate, pediatric patients will be included in all discussions. This can be accomplished through one of the following mechanisms: a) the NCI POB screening protocol, b) an IRB-approved institutional screening protocol, or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient s research chart. Studies or procedures that were performed for clinical indications (not

Trial name: SPRINT Phase 2 Stratum I	NCT number: NCT01362803

exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

12. Willingness to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.
13. Willingness to avoid the ingestion of grapefruit and Seville oranges (as well as other products containing these fruits, e.g. grapefruit juice or marmalade) during the study, as these may affect selumetinib metabolism.

Main exclusion criteria

1. Pregnant or breast-feeding females are excluded due to potential risks of fetal and teratogenic adverse events of an investigational agent. Pregnancy tests must be obtained prior to enrollment for all females of childbearing potential as per institutional standards (at NIH subjects 9 years and older or those showing pubertal development). Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method. Abstinence is an acceptable method of birth control.
2. Phase I: Patients who anticipate the need for surgical intervention within the first three cycles (3 months), as surgical intervention during the period of DLT evaluation may affect analysis of adherence and/or make the subject inevaluable.
3. Use of an investigational agent within the past 30 days.
4. Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, immunotherapy, or biologic therapy.
5. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses, or renal transplant, including any patient known to have hepatitis C, or human immunodeficiency virus (HIV) will be excluded. Patients with HIV who have adequate CD4 count, not requiring antiretroviral medication, may be enrolled.
6. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study.
7. Inability to swallow capsules, since capsules cannot be crushed or broken.
8. Inability to undergo MRI and/or contraindication for MRI examinations following the MRI protocol. Prosthesis or orthopedic or dental braces that would interfere with volumetric analysis of target PN on MRI.
9. Refractory nausea and vomiting, chronic grastointestinal disease (e.g., inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption.
10. Prior treatment with selumetinib or another specific MEK1/2 inhibitor (unless the subject meets criteria for re-treatment.
11. Evidence of an optic glioma, malignant glioma, malignant peripheral nerve sheath tumor, or other cancer requiring treatment with chemotherapy or radiation therapy.
12. Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must be stopped prior to initiation of therapy.
13. Patients not achieving adequate blood pressure in spite of antihypertensive therapy for control of blood pressure.
14. Cardiac Function: a) known inherited coronary disease, b) Symptomatic heart failure (NYHA Class II-IV prior or current cardiomyopathy, or severe valvular heart disease), c) Prior or current cardiomyopathy, d) Sever valvular heart disease, 3) History of atrial fibrillation
15. Ophthalmologic conditions:
16. Current or past history of central serous retinopathy
17. Current or past history of retinal vein occlusion

Trial name: SPRINT Phase 2 Stratum I	NCT number: NCT01362803

18. Known intraocular pression (IOP) greater than 21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP); Patients with known glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) and are not experiencing pain related to the glaucoma, may be eligible after discussion with the study chair.
19. Subjects with any other significant abnormality on ophthalmic examination should be discussed with the Study Chair for potential eligibility
20. Ophthalmological f ndings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study
21. Known severe hypersensitivity to selumetinib or any excipient of selumetinib or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib.
22. Recent major surgery within a minimum of 4 weeks prior to starting study treatment, with the exception of surgical placement for vascular access.
23. Any unresolved chronic toxicity with CTC AE grade greater than or equal to 2 from anti-NF1 therapy, except for alopecia.
24. Clinical judgement by the investigator that the patient should not participate in the study.
25. While not an exclusion criterion, unless considered clinically indicated, patients should avoid taking other additional non-study medications that may interfere with the study medications. In particular, patients should avoid medications that are known to either induce or inhibit the activity of hepatic mircrosomal isoenzymes CYP1A2, CYP2C19 and CYP3A4, as this may interfere with the metabolism of selumetinib.

Intervention	Selumetinib orally 25 mg/m^2 BSA, BID
Comparator(s)	N/A – single-arm trial External controls: • NCI Natural History study (NCT00924196) • Placebo arm of the tipifarnib NF1 study (01-C-0222, NCT00021541)
Follow-up time	Median duration of follow-up at 29th March 2019 DCO was 3 years [42]; some endpoints have also been reported at 5 years of follow-up (27th February 2021 DCO) by NCI [78]. 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
Is the study used in the health economic model?	Yes

Trial name: SPRINT Phase 2 Stratum I	NCT number: NCT01362803
Primary endpoints	**Tumour volumetric response** • ORR to selumetinib, defined as the rate of confirmed PR and CR (CR defined as the disappearance of the target PN; PR defined as PN decrease ≥20% compared to baseline) using centrally read volumetric MRI
Secondary endpoints	**Tumour volumetric response** • BOR to selumetinib • Duration of response to selumetinib, in patients with confirmed PR • Effect of selumetinib on PN growth rate • TTP and PFS in progressive PN **Clinical outcome measures** • Effect of selumetinib on QoL (PedsQL) • Effect of selumetinib on pain (NRS-11, PII, pain medication survey) • Effect of selumetinib on physical functioning (6MWT) • Effect of selumetinib on impairments secondary to PN, and functional outcomes dependent on PN location • Effect of selumetinib on disfigurement (Photography) **Global impression of change** • Global impression of change (GIC) in tumour pain, overall pain, and tumour-related morbidities compared to baseline
Safety	• Long-term tolerability and safety of selumetinib • Incidence of adverse events
Method of analysis	All the efficacy analysis were ITT analysis. Simple cumulative probability was applied to estimate the progression rate of PN, and the Weibull distribution was applied to estimate the TTD.
Subgroup analyses	N/A
Other relevant information	N/A

Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Below in Table 64 are presented the baseline characteristics of patients included in the studies used in the comparative analysis.

Table 64. Patient characteristics in Danish cohort study, SPRINT, NCI NH age matched cohort and Tipifarnib 01-C0222 placebo arm.

	Variable	Danish National cohort Study [50]	NCI Natural History Study of Patients with NF1 (Age matched 1:1 cohort)	SPRINT Phase 2 Stratum I	Tipifarnib 01-C0222 placebo arm [77]
Sex n (%)	Female	20 (62)	14 (38.9)	20 (40.0)	14 (48.27)
	Male	12 (38)	22 (61.1)	30 (60.0)	15 (51.73)
Race n (%)	White	-	29 (80.6)	42 (84.0)	-
	Other	-	7 (19.4)	8 (16.0)	-
Age (years)	Mean, SD	6.3 (3.7)	9.9 (4.14)	10.3 (3.92)	-
Age (years)	Median (range)	-	-	10.2 (3.5-17.4)	8.2 (3-17.7)
Weight (kg)	Mean, SD	-	33.2 (16.48)	34.9 (16.48)	-
Height (cm)	Mean, SD	-	132.6 (22.98)	133.8 (21.02)	-
Target PN volume (L)	Mean, SD	-	0.6 (0.68)	0.8 (0.93)	0.527(0.0205–5.573)[a]
Target PN size (cm)	Mean, SD	4.5 (2.5)	-	-	-
Target PN location n (%)	Head/Neck/ Trunk	24 (52)	18 (50.0)	29 (58.0)	16 (51.6)
	Trunk/Extremity/ Whole Body	22 (48)	18 (50.0)	21 (42.0)	15 (48.4)

[a]The study of Widemann et al. 2014 [77] reported the median PN volume and the range instead of the mean and the SD.

Comparability of patients across studies

SPRINT Phase 2 Stratum I vs NH study

As mentioned in Section 7.1.2, non-randomised comparisons vs external controls were performed in order to determine the comparative effectiveness of selumetinib vs relevant comparators. Given that SPRINT Phase 2 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 2 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 2 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 2 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 2 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 [42, 71].

In addition, in order to directly compare the data in the age-matched cohort to the data from SPRINT Phase 2 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 [42, 71]. Please note that patients were not required to be under risk for 3.2 years as this may introduce survival bias.

SPRINT Phase 2 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 [[77]]. This is in comparison to SPRINT Phase 2 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 2 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 2 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 2 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 2 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 2 Stratum I with progressive PN at study entry, and to the full cohort of 50 patients enrolled in SPRINT Phase 2 Stratum I.

Appendix D – Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 65 shows the outcome measures included in the SPRINT Phase 2 Stratum I trial. The objective response rate (ORR), progression-free survival (PFS) and PN growth rate outcome measures were also reported for the age-matched Natural History cohort. PFS was also reported for the placebo arm of the tipifarnib Study 01-C-0222.

Table 65. Outcome measures of SPRINT Phase 2 Stratum I trial

Outcome measure	Definition	Clinical relevance
Primary endpoint		The most clinically relevant PN was selected at baseline by the treating physician as the 'target lesion' and was used to determine treatment response. The target PN was required to be amenable to volumetric MRI assessment.
Objective response rate (ORR) to selumetinib	Percentage of patients with complete response (CR) or confirmed partial response (cPR) using centrally read volumetric MRI. CR was defined as the disappearance of the target PN. 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 confirmed (cPR) when observed on consecutive restaging examinations at least 3 months apart.	
Secondary endpoints (tumour volumetric responses)		
Best objective response (BOR) to selumetinib	The best response recorded from the start of treatment until progression or the last evaluable volumetric MRI assessment in the absence of progression.	
Duration of response to selumetinib in patients with confirmed PR	The time the response lasted.	
Effect of selumetinib on PN growth rate	The change (%) in target PN volume over time in patients receiving selumetinib.	

Outcome measure	Definition	Clinical relevance
Time to progression (TTP) and progression-free survival (PFS) in progressive PN (≥20% increase in PN volume within 12–15 months prior to enrolment)	In the 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.	
Progression free-survival (PFS)	The time from study treatment initiation until the pre-cycle of objective progression or death (by any cause in the absence of progression).	
Secondary endpoints (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 assessments were collected irrespective of patients' baseline PN-associated morbidities. Functional assessments were collected only from patients with those morbidities at baseline. The primary analysis of the clinical outcome measures was based on descriptive statistics and mixed model repeated measures (MMRM) analyses summarizing the changes over time. MMRM analyses were used to allow for correlation between observations within a subject. Supportive analyses using clinically meaningful thresholds (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 global impression of change as the anchor) approaches. Whenever available, data from published literature were used to define the CMT. The CMT definitions were as follows:
Effect of selumetinib on HRQoL	Paediatric Quality of Life Inventory (PedsQL) total score and the four domain scores: Physical functioning, emotional functioning, social functioning, school functioning.	
Effect of selumetinib on pain	Numerical rating scale 11 (NRS-11), pain interference index (PII), pain medication survey.	
Effect of selumetinib on motor function	Patient-reported Outcomes Information System (PROMIS, mobility and upper extremity), strength, range of motion, grooved pegboard test, grip strength and key pinch, leg length evaluation.	
Effect of selumetinib on airway function	Apnoea hypopnea index (AHI) sleep study, pulmonary function tests (PFTs).	
Effect of selumetinib on bowel/bladder function	Dysfunctional voiding questionnaire (DVQ).	
Effect of selumetinib on visual function	Visual acuity, exophthalmometry.	
Effect of selumetinib on physical functioning	Six-minute walk test (6MWT), only in patients with lower extremity PN, cord compression or airway PN.	

Outcome measure	Definition	Clinical relevance
Effect of selumetinib on disfigurement	Captured via photography.	• Improvement: a change from baseline ≥ CMT points • Deterioration: a change from baseline ≤ −CMT points • No change: a change from baseline between (−CMT to CMT)
Global impression of change (GIC)	A GIC scale was used to assess change in tumour pain, overall pain and tumour-related morbidities compared to baseline.	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.
Long-term tolerability and safety of selumetinib	Detailed clinical evaluation, laboratory studies, electrocardiogram/echocardiogram (ECG/ECHO) or cardiac MRI, ophthalmologic exams, symptoms check-list, patient diary, adverse events (AEs).	-
Other secondary outcomes		
Bone mineral density in patients with impaired bone mineral density at the time of enrolment[a]	-	-
Day one and steady state pharmacokinetics of selumetinib[b]	-	-
Changes in the size of the optic pathway tumours or other glioma[c]	-	-
Changes in ERK phosphorylation in peripheral blood mononuclear cells (PBMCs)[d]	-	-

[a]Data on bone mineral density have not been presented within this submission, as the results are not relevant for the scope of this appraisal. [b]Pharmacokinetic analyses are included in the SPRINT CSR, but have not been presented within this submission as these results are not relevant for the scope of this appraisal. [c]This objective was of an exploratory nature for research purposes, and data were not collected in the clinical database. [d]There was insufficient viable data for this objective to be included in the SPRINT CSR.

Table 66 shows the results of the outcome measures reported for both the SPRINT Phase 2 Stratum I trial and one of the external controls (either the age-matched Natural History cohort or the placebo arm of the tipifarnib Study 01-C-0222). The probability of PFS at 3 years from the SPRINT Phase 2 Stratum I trial was used in the health economic analysis. ORR and PN growth rate results could not be included in the health economic analysis as it was not possible to establish a robust association between target PN volume or another surrogate endpoint and HRQoL (see Section 8.4.1). Nonetheless, they are still considered relevant due to the availability of comparative data. For a detailed description of all the outcome measures results, including safety results, see Section 7.1.2.

Table 66. Outcome measures for the SPRINT Phase 2 Stratum I trial and NCI Natural History study (age matched cohort)

Outcome measures results						
Outcome	**Study**	**N**	**Result (CI)**	**Follow-up**	**Description of methods used for estimation**	**References**
ORR	SPRINT Phase 2 Stratum I (NCT01362803)	50	68%	3.2 years	Naïve comparison. ORR, defined as the rate of confirmed PR and CR, was assessed using volumetric magnetic resonance imaging analysis.	[42]
	Age-matched Natural History cohort (NCT00924196)	93	0%			
PN growth rate						
Patients with a PN growth rate ≥20% per year, % (n)	SPRINT Phase 2 Stratum I (NCT01362803)	50	0 (0)	3.2 years	Naïve comparison. PN were assessed using volumetric magnetic resonance imaging and progression was determined by a PN volume increase of ≥20% in at least one PN compared with baseline.	[42]
	Age-matched Natural History cohort (NCT00924196)	93	43 (40)			
Median change in PN volume, between baseline and most recent MRI, % (range)	SPRINT Phase 2 Stratum I (NCT01362803)	50	-23 (-55.1 – +30)	3.2 years	Naïve comparison. PN were assessed using volumetric magnetic resonance imaging and progression was determined by a PN volume increase of ≥20% in at least one PN compared with baseline	[42]
	Age-matched Natural History cohort (NCT00924196)	93	+77 (-40 – +1,429)			

Progression-free survival						
Median PFS, years (95% CI)	SPRINT Phase 2 Stratum I (NCT01362803)	50	N/A[a]	3.2 years	Median PFS was not reached in SPRINT Phase 2 Stratum I. Based on the Kaplan-Meier estimates, , there was a continued divergence in PFS between patients receiving selumetinib in SPRINT Phase 2 Stratum I and patients in the NH Study age-matched cohort, over the duration of the follow-up period.	[42]
	Age-matched Natural History cohort (NCT00924196)	93	1.3 (1.1–1.6)			
Probability of PFS at 3 years, %	SPRINT Phase 2 Stratum I (NCT01362803)	50	84	3.2 years	Progression was identified through PN growth, which was assessed using volumetric magnetic resonance imaging. After 3 years, 84% of the patients enrolled in SPRINT were progression free.	[42]
	Age-matched Natural History cohort (NCT00924196)	93	15			
Probability of PFS at 2 years, % (95% CI)[b]	SPRINT Phase 2 Stratum I (NCT01362803)	21[c]	88.9 (62.4–97.1)	2 years	Naïve comparison. Progression was identified through PN growth, which was assessed using volumetric magnetic resonance imaging. Progression was determined by a PN volume increase of ≥20% in at least one PN compared with baseline	[71]
	Placebo arm of the tipifarnib Study 01-C-0222	29[d]	21 (7.7–37.8)			[77]

[a]The median PFS has not yet been reached, with only 12% of patients experiencing disease progression (6/50). At the 27th of February 2021 DCO, five years since the start of treatment, median PFS in SPRINT Phase 2 Stratum I was still not reached [78].

Appendix E – Safety data for intervention and comparator

See Section 7.

Appendix F – External control: Natural History study propensity score matched analysis

Propensity score analysis was performed for the comparison of PFS between selumetinib-treated patients from SPRINT Phase 2 Stratum I vs patients treated with established clinical management only from the NH study [107, 108]. Propensity score analyses were explored to understand the potential impact of adjusting for baseline covariates across the study populations on estimates of treatment effect [107, 108]. Propensity score matching is a well-documented approach for reducing this risk of bias [109]. The propensity score is defined as the probability of being treated, conditional on observed baseline characteristics (covariates) [110]. This score can be used to balance the covariates between two groups, reducing bias in comparisons accordingly [107, 108].

Four different methods were performed to investigate the risk of bias for the comparison of the SPRINT Phase 2 Stratum I and Natural History study populations:

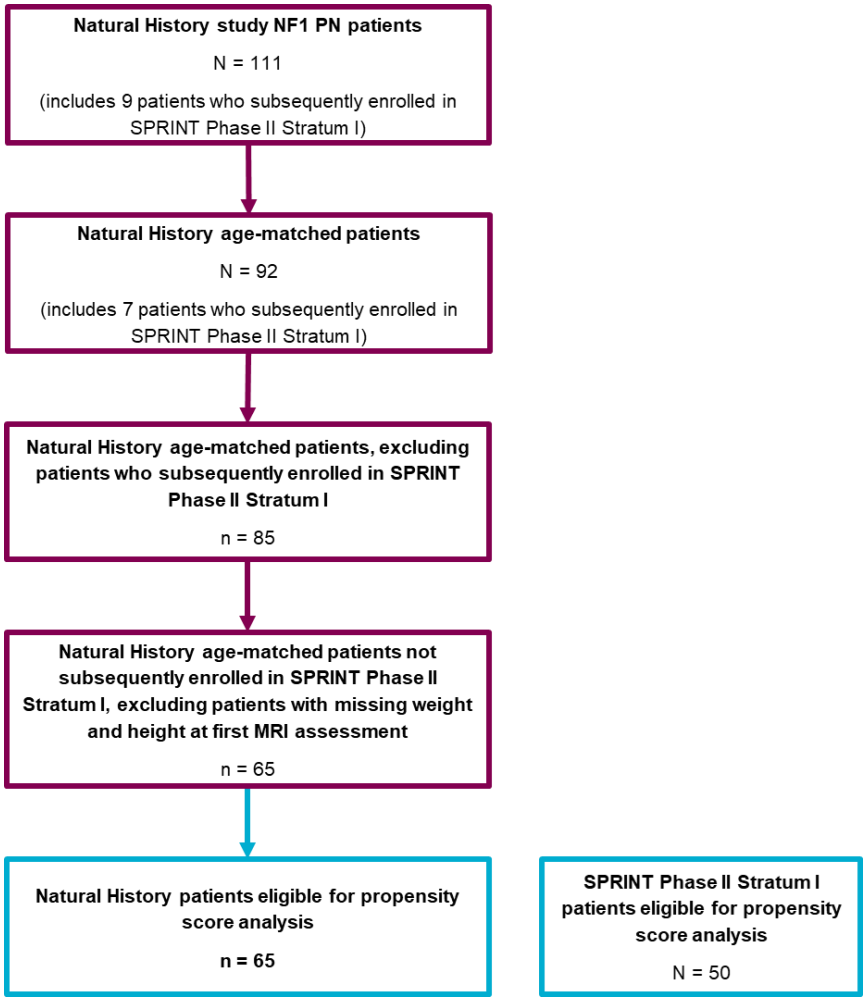
1. Matched 1:1 (without replacement) with a robust variance
2. Weighted using stabilised Inverse Probability of Treatment Weighting (IPTW)
3. Weighted using IPTW, with a robust variance
4. Matched 1:2 (with replacement) with a robust variance

As these analyses were performed by AstraZeneca, they were based on the PFS data reported in the SPRINT CSR (DCO 29th June 2018) [71].

Patient eligibility

Data were complete for all 50 patients in SPRINT Phase 2 Stratum I, therefore, all patients were considered in the analysis. A small number of patients who were included in the NH age-matched cohort were subsequently enrolled in SPRINT (n=7). To maintain independency between the two studies, data for these seven patients were excluded for the NH arm of this comparison. Patients with missing weight and height at first MRI assessment of target PN (n=20) were also excluded. Sixty-five patients from the NH study were ultimately eligible for propensity score analysis. A flow chart demonstrating patient eligibility is presented in Figure 32.

Figure 32. Propensity score analysis patient eligibility flowchart



Propensity score matching 1:1 (without replacement)

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

- The study (SPRINT Phase 2 Stratum I for selumetinib treatment, NH 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) [111].
- 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 NH 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, 36 patients from the SPRINT study were matched to 36 eligible patients from the Natural History study using the propensity scores.

Inverse probability of treatment weighting (IPTW)

Each patient from the SPRINT Phase 2 Stratum I (selumetinib-treated) and eligible NH study (established clinical management) was assigned a weight based on the inverse of the propensity score. Stabilised weights were used 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 2 for the NH 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 [112].

As a sensitivity analysis, each patient from the SPRINT Phase 2 Stratum I was matched to up to two eligible patients from the NH study using the propensity scores. Matches were found for 47 patients from SPRINT Phase 2 Stratum I, with replacement (i.e., eligible patients from the NH study could have been used multiple times). These matches were based on 41 unique eligible patients from the NH 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 [113]. Concerning the full details of the propensity score matching, of the 47 SPRINT patients:

- 46 of the 47 SPRINT patients were matched exactly to 2 NH patients;
- 1 SPRINT patient was matched to 1 NH patient.

Of the 41 NH patients,

- 20 NH patients were each matched to 1 SPRINT patients;
- 10 NH patients were each matched to 2 different SPRINT patients;
- 2 NH patients were each matched to 3 different SPRINT patients;
- 4 NH patients were each matched to 4 different SPRINT patients;
- 2 NH patients were each matched to 5 different SPRINT patients;
- 3 NH patients were each matched to 7 different SPRINT patients.

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 67.

Baseline characteristics were compared between SPRINT Phase 2 Stratum I and the NH study by calculating standardised difference, defined as the absolute difference in sample means (for continuous variables) or proportions (for binary variables) over the pooled standard deviation (SD) of the variable.

Before matching/weighting:

- SPRINT Phase 2 Stratum I and the NH study had similar proportions of female and male patients and of White, Asian and Black or African American patients.

- The NH study had more patients with PN in the trunk alone, whilst SPRINT Phase 2 Stratum I had more patients with PN in the head or head/neck. Patients in SPRINT Phase 2 Stratum I were slightly older, heavier, taller and had a larger PN volume at baseline. Standardised differences that are <0.1 or <0.2 can been considered small [114]. The standardised difference for age was 0.289.

After matching/weighting, baseline characteristics were similar between SPRINT Phase 2 Stratum I and the NH study, as shown by reduced standardised differences. However, the matched analyses did result in a reduction in the sample sizes.

Table 67. Baseline characteristics for all patients included in the propensity score analysis pre matching/weighting, and after propensity score matching/weighting

Variable		Pre-matching/weighting			1:1 matching			Stabilised IPTW			1:2 matching		
		SPRINT (N=50)	NH (N=65)	Std. Diff.	SPRINT (N=36)	NH (N=36)	Std. Diff.	SPRINT (Sum of weights =50.6)	NH (Sum of weights =64.5)	Std. Diff.	SPRINT (N=47)	NH (N=41)	Std. Diff.
Sex n (%)	Female	20 (40.0)	24 (36.9)	0.063	14 (38.9)	14 (38.9)	0.000	19.5 (38.5)	24.9 (38.7)	0.004	19 (40.4)	17 (42.6)	0.043
	Male	30 (60.0)	41 (63.1)		22 (61.1)	22 (61.1)		31.1 (61.5)	39.5 (61.3)		28 (59.6)	24 (57.4)	
Race n (%)	White	42 (84.0)	51 (78.5)	0.142	28 (77.8)	29 (80.6)	0.068	39.7 (78.4)	50.9 (78.9)	0.013	39 (83.0)	35 (85.1)	0.058
	Other	8 (16.0)	14 (21.5)	0.275	8 (22.2)	7 (19.4)		10.9 (21.6)	13.6 (21.1)		8 (17.0)	6 (14.9)	
Age (years)	Mean, SD	10.3 (3.92)	9.2 (4.12)	NR	10.1 (3.95)	9.9 (4.14)	0.051	9.5 (3.96)	9.6 (4.23)	0.032	10.1 (3.92)	10.1 (2.70)	0.003
Weight (kg)	Mean, SD	34.9 (16.48)	31.5 (16.73)	0.205	35.9 (17.90)	33.2 (16.48)	0.161	32.8 (16.29)	33.3 (17.54)	0.031	35.0 (16.91)	32.8 (10.20)	0.160
Height (cm)	Mean, SD	133.8 (21.02)	129.0 (23.34)	0.214	134.4 (20.98)	132.6 (22.98)	0.085	130.4 (21.34)	131.4 (23.72)	0.041	133.7 (21.46)	133.1 (14.90)	0.033
Target PN volume (L)	Mean, SD	0.8 (0.93)	0.6 (0.80)	0.260	0.7 (0.71)	0.6 (0.68)	0.160	0.7 (0.80)	0.7 (0.93)	0.021	0.7 (0.76)	0.8 (0.54)	0.11
Target PN location n (%)	Head/Neck/ Trunk	29 (58.0)	23 (35.4)	0.465	16 (44.4)	18 (50.0)	0.111	21.9 (43.3)	28.0 (43.4)	0.003	26 (55.3)	21 (52.1)	0.064
	Trunk/Extremity/ Whole Body	21 (42.0)	42 (64.6)		20 (55.6)	18 (50.0)		28.7 (56.7)	36.5 (56.6)		21 (44.7)	20 (47.9)	

Source: AstraZeneca Data on File (Propensity Score Analysis Report; DCO 29th June 2018) [115].

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 68). The results were highly consistent across all four additional analyses, demonstrating a high degree of robustness to the choice of method used for comparison.

Table 68. HR for PFS for the naïve comparison and for the propensity score analyses

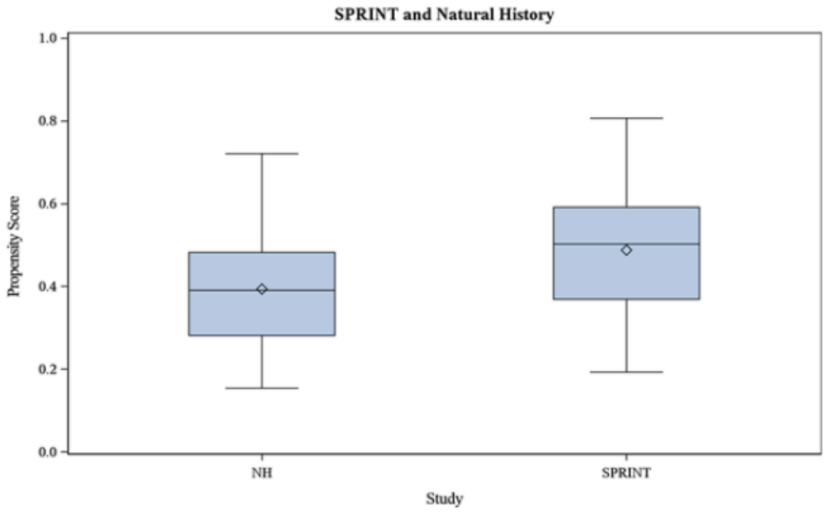
Analysis	Hazard Ratio[d]	95% CI	p-value
Cox model: Naïve comparison	0.07	0.02, 0.24	<0.001

Cox model: Matched patients 1:1 (robust variance estimator)[a,b]	0.08	0.02, 0.29	<0.001
Cox model: Weighted by stabilised IPTW	0.09	0.03, 0.27	<0.001
Cox model: Weighted by IPTW (robust variance estimator)	0.09	0.03, 0.29	<0.001
Cox model: Matched patients 1:2 (robust variance estimator)[b,c]	0.09	0.03, 0.24	<0.001

[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. [d]HRs were obtained using Cox regression with study as the only covariate.
Source: AstraZeneca Data on File (Propensity Score Analysis Report) [115].

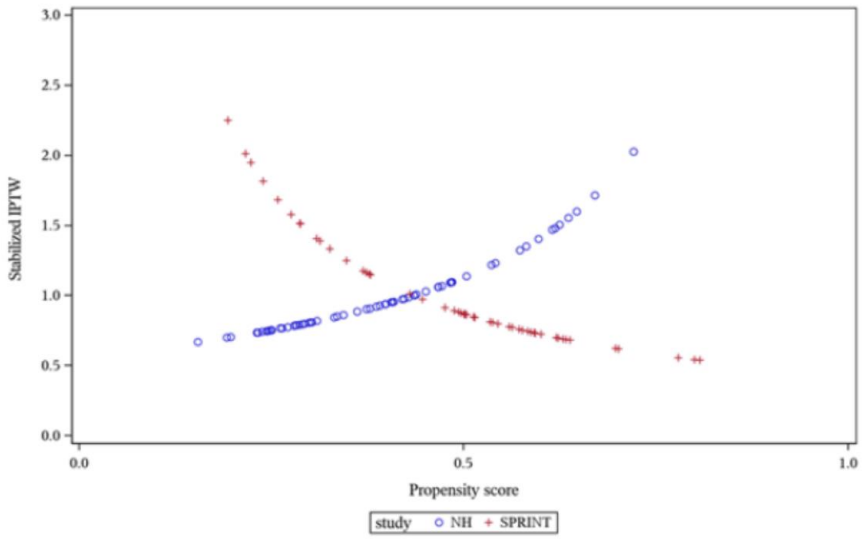
Distribution of propensity score by study is described in Figure 33, while Figure 34 shows the distribution of the weights by propensity score and study. No weights were >3 for SPRINT or >2 NH, respectively. Table 69 shows propensity score analyses demonstrating a mean difference in annual PN growth rate between untreated patients from the NH Study and treated patients from SPRINT phase 2 stratum 1 of 35.3% to 38.6%. Kaplan-Meier curves for the naïve, weighted, matched 1:1 without replacement, stabilised IPTW and matched 1:2 with replacement analyses are presented in Figure 35.

Figure 33. Distribution of propensity scores by study



Propensity scores are obtained by a logistic regression including sex, race, PN location and baseline age, weight, height and PN volume. NH: Natural history; PN: Plexiform neurofibromas.
Source: AstraZeneca Data on File (Propensity Score Analysis Report) [115].

Figure 34. Distribution of weights by propensity score and study



Propensity scores are obtained by a logistic regression including sex, race, PN location and baseline age, weight, height and PN volume. IPTW: inverse probability of treatment weighting; PN: Plexiform neurofibromas.
Source: AstraZeneca Data on File (Propensity Score Analysis Report) [115].

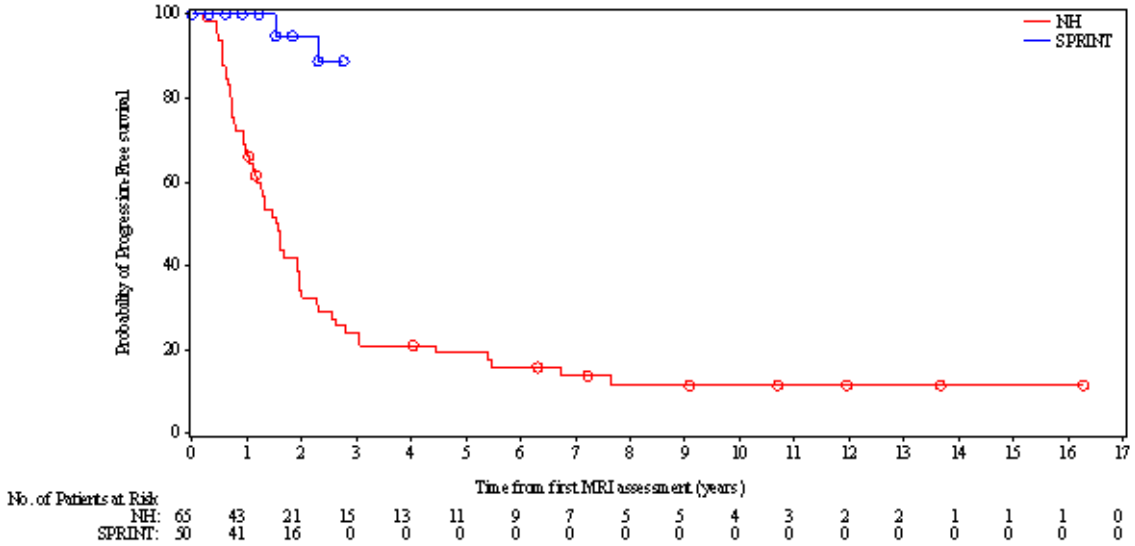
Table 69. Percentage change in target PN volume (mean difference by propensity score adjustment method) – SPRINT Phase II Stratum I vs Natural History comparator cohort

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	36	1.9 (1.6,2.1)	-7.6 (-11.0,-4.2)	-15.8 (-20.1.-11.6)
	Natural H	37	6.2 (4.9,7.4)	20.9 (12.6,29.3)	19.5 (12.6,26.4)
	Adjusted mean difference				-35.3 (-43.1,-27.6)
1 :2 match	SPRINT	44	1.9 (1.7,2.1)	-8.8 (11.8,-5.9)	-17.5 (-21.1,-13.8)
	Natural H	43	6.7 (5.6,7.9)	20.7 (12.9,28.5)	21.2 (15.4,26.9)
	Adjusted mean difference				-38.6 (-45.2,-32.0)
IPTW	SPRINT	48	1.8 (1.7,2.0)	-9.4 (12.2,6.5)	-16.2 (-19.6,-12.8)
	Natural H	7.5	6.7 (6.2,8.2)	21.6 (15.6,27.6)	15.1 (15.1,23.8)
	Adjusted mean difference				-35.7 (-41.1,-30.3)
Stabilised IPTW'	SPRINT	48	1-8 (1.7. 2.0)	-9.4 (-12.2,-6.5)	-16.2 (-19.6,-12.8)
	Natural History	75	6.7 (6.2,8.2)	21.6 (15.6,27.6)	15.1 (15.1,23.8)
	Adjusted mean difference				-35.7 (-41.1,-30.3)

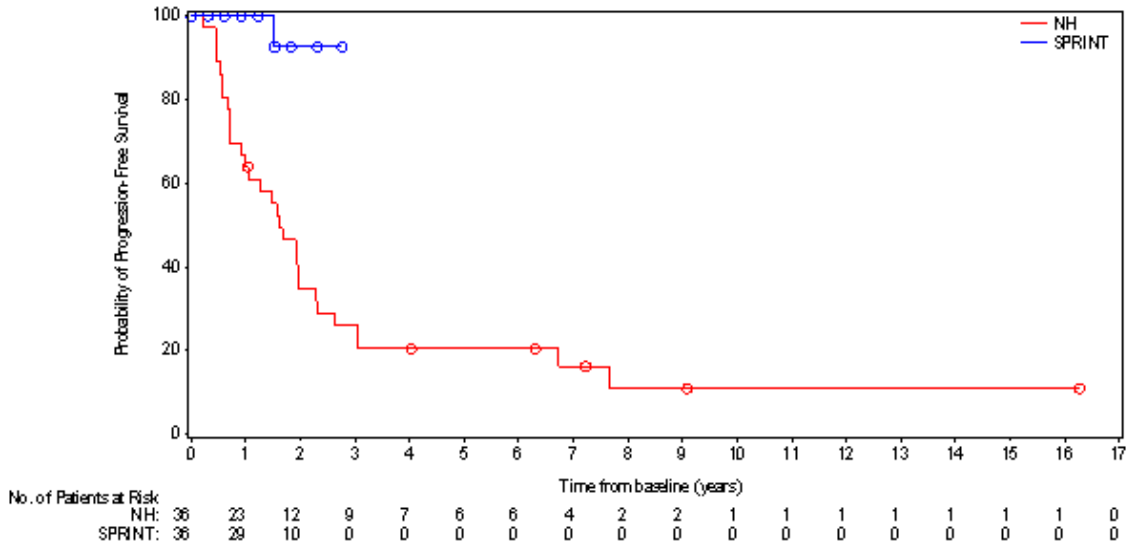
CI: confidence interval; IPTW: inverse probability of treatment weighting; PN: plexiform neurofibroma.

Figure 35. Kaplan-Meier curves for the naïve, matched 1:1, stabilised IPTW, and 1:2 analyses

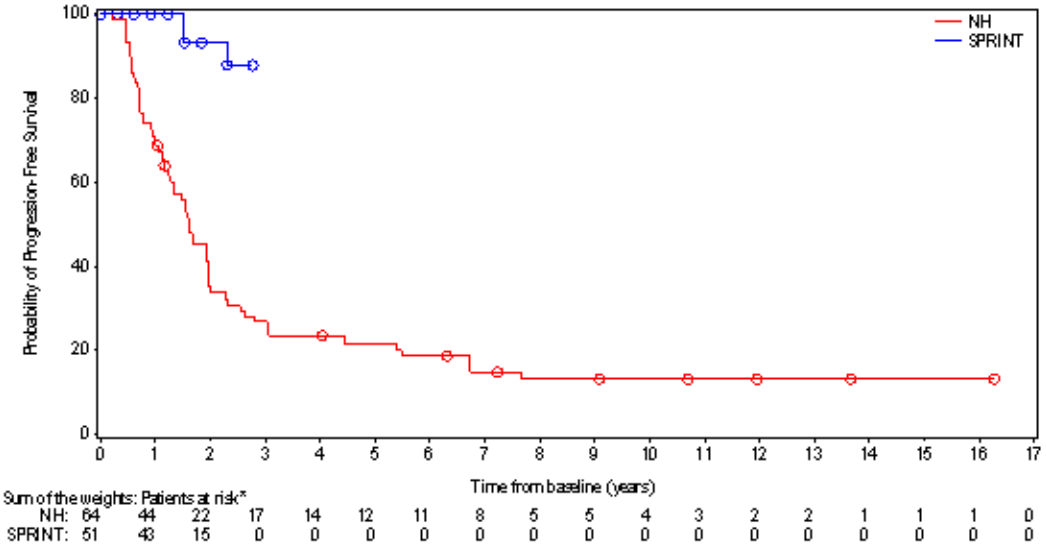
Naïve analysis



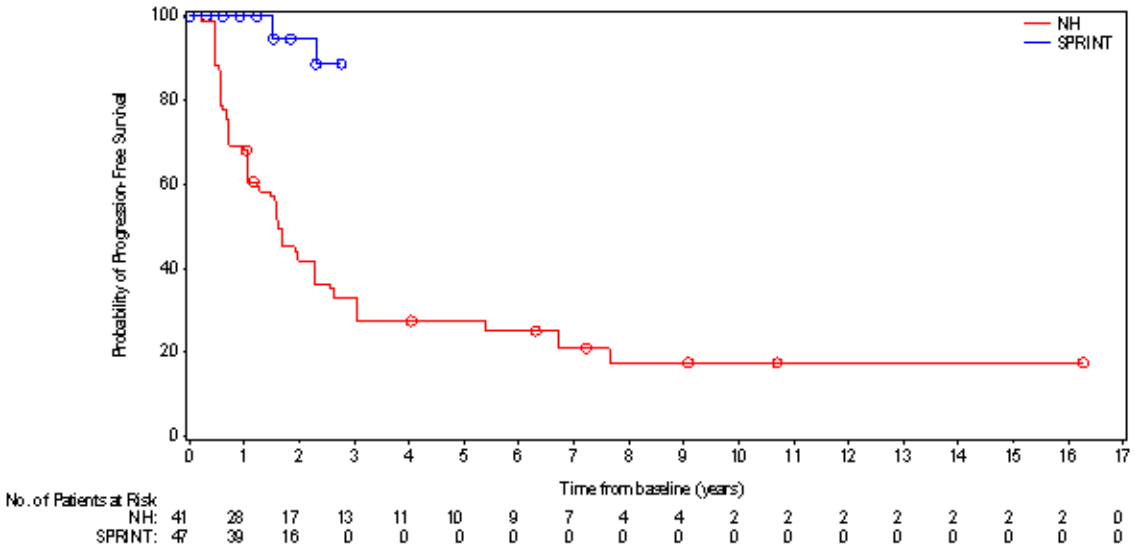
Matched 1:1



Stabilised IPTW



Matched 1:2 with 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.
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.
Source: AstraZeneca Data on File (Propensity Score Analysis Report) [115].

Appendix G – Extrapolation

See Section 8.3

Appendix H – Literature search for HRQoL data

In total, 18 publications were identified covering fifteen unique studies. The number of records included and excluded at each SLR stage are presented in figure 33. We do not find anything relevant to include for selumitinib in the application.
The search terms used in MEDLINE, Embase, Cochrane, INAHTA and Econlit can be seen in tables 68 to 71. A summary of the studies included in the HRQoL SLR reporting can be found in Table 76.

Table 70. Search terms used in MEDLINE (searched via Ovid SP on 7th September 2022)

#	Searches	Results
1	exp Neurofibromatosis 1/	10517
2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kf.	8788
3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kf.	9393
4	or/1-3	17852
5	Cost-benefit analysis/	90599
6	"Costs and cost analysis"/	50839
7	Economics/	27465
8	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).ti,ab,kf.	177998
9	(economic evaluation$ 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$).ti,ab,kf.	42868
10	Quality-adjusted life years/	15067
11	Value of life/	5793
12	or/5-11	307634
13	(health utilit$ 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.	11681
14	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	1056
15	(multiattribute$ or multi attribute$).ti,ab.	1140
16	utility.ab. /freq=2	21857
17	(utilities or disutilit$).ti,ab,kf.	9140
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.	15088
19	(short form$ or shortform$).ti,ab.	40991
20	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	25410
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.	3799
22	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.	5892

23	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.	32
24	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.	353
25	(15D or 15-D or 15 dimension).ti,ab,kf.	5911
26	visual analog$ scale$.ti,ab,kf.	68366
27	(standard gamble$ or sg).ti,ab,kf.	13194
28	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	2226
29	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kf.	84
30	(hui or hui1 or hui2 or hui3 or rosser).ti,ab,kf.	1960
31	*quality of life/ and (quality of life or qol or hrqol).ti,ab,kf.	90647
32	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	37552
33	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).ti,ab,kf.	17349
34	quality of life/ and health-related quality of life.ti,ab,kf.	41559
35	quality of life/ and ec.fs.	10875
36	quality of life/ and (health adj3 status).ti,ab,kf.	11085
37	((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ 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.	49166
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.	75196
39	or/13-38	367083
40	Cost allocation/	2015
41	Cost control/	21652
42	Cost savings/	12620
43	Cost of illness/	30928
44	Cost sharing/	2695
45	"Deductibles and coinsurance"/	1842
46	Medical savings accounts/	547
47	Health care costs/	43482
48	Direct service costs/	1217
49	Drug costs/	17244
50	Employer health costs/	1097
51	Hospital costs/	11871

52	Health expenditures/	23279
53	Capital expenditures/	2001
54	exp economics, Hospital/	25621
55	exp economics, Medical/	14360
56	Economics, nursing/	4013
57	Economics, pharmaceutical/	3079
58	exp Budgets/	14042
59	Financial management/	16940
60	exp "Fees and charges"/	31192
61	(low adj cost).mp.	78435
62	(high adj cost).mp.	18223
63	(health?care adj cost$).mp.	15124
64	(fiscal or funding or financial or finance).ti,ab,kf.	185725
65	(cost adj estimate$).mp.	2617
66	(cost adj variable$).mp.	187
67	(unit adj cost$).mp.	2959
68	(economic$ or pharmacoeconomic$ or price$ or pricing).ti,ab,kf.	400432
69	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).ti,ab,kf.	129965
70	((patient$ or caregiver$ or carer$ or social$ or society$ or family$ or work$) adj2 (burden$ or productiv$)).ti,ab,kf.	26191
71	("length of stay" or utili?ation or "economic burden" or "cost-of-illness" or nursing cost$ or physician cost$ or physician visit$ or "out of pocket").ti,ab,kf.	339188
72	(absenteeism or presenteeism or employment or unemployment).ti,ab,kf. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	163152
73	or/40-72	1295265
74	exp animals/ not exp humans/	5042506
75	(comment or editorial).pt.	1402101
76	historical article/	368692
77	or/74-76	6738326
78	4 and (12 or 39 or 73)	420
79	78 not 77	406
80	limit 79 to yr="2021 -Current"	83

Search terms used in Embase (searched via Ovid SP on 7th September 2022)

Table 71. Search terms used in Embase (searched via Ovid SP on 7th September 2022)

#	Searches	Results
1	exp neurofibromatosis type 1/	4913

2	(neurofibroma$ adj2 ("1" or i or peripheral or von Recklinghausen)).ti,ab,kw.	11209
3	(NF1 or NFI or NF-1 or NF-I).ti,ab,kw.	14059
4	or/1-3	19445
5	Cost benefit analysis/ or exp economic evaluation/ or cost effectiveness analysis/ or cost minimization analysis/ or cost benefit/	339283
6	Economics/ or health economics/ or socioeconomics/ or economic aspect/ or pharmacoeconomics/	527502
7	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).ti,ab,kw.	239884
8	(economic evaluation$ 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$).ti,ab,kw.	64693
9	Quality adjusted life year/	32386
10	or/5-9	919191
11	(health utilit$ 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.	19388
12	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kw.	1582
13	(multiattribute$ or multi attribute$).ti,ab.	1351
14	utility.ab. /freq=2	33795
15	(utilities or disutilit$).ti,ab,kw.	14696
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.	27199
17	(short form$ or shortform$).ti,ab.	55594
18	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	43392
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.	5174
20	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kw.	9871
21	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kw.	58
22	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kw.	368
23	(15D or 15-D or 15 dimension).ti,ab,kw.	7335
24	visual analog$ scale$.ti,ab,kw.	95703
25	(standard gamble$ or sg).ti,ab,kw.	19479
26	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	3278
27	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kw.	170
28	(hui or hui1 or hui2 or hui3 or rosser).ti,ab,kw.	2981
29	*quality of life/ and (quality of life or qol or hrqol).ti,ab,kw.	117696

30	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw.	92919
31	quality of life/ and ((quality of life or qol or hrqol) adj (score$1 or measure$1)).ti,ab,kw.	35599
32	quality of life/ and health-related quality of life.ti,ab,kw.	71679
33	quality of life/ and ec.fs.	53749
34	quality of life/ and (health adj3 status).ti,ab,kw.	18623
35	((qol or hrqol or quality of life).ti,kw. or *quality of life/) and ((qol or hrqol$ 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.	69625
36	(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,kw.	115014
37	or/11-36	601868
38	Cost control/	74043
39	Cost of illness/	20755
40	Health care cost/	214274
41	Drug cost/	83549
42	Hospital cost/	24168
43	exp Budget/	32192
44	Financial management/	118773
45	health care financing/	13883
46	exp Fee/	42807
47	(low adj cost).mp.	86281
48	(high adj cost).mp.	23778
49	(health?care adj cost$).mp.	26283
50	(fiscal or funding or financial or finance).ti,ab,kw.	261676
51	(cost adj estimate$).mp.	3979
52	(cost adj variable$).mp.	305
53	(unit adj cost$).mp.	5236
54	(economic$ or pharmacoeconomic$ or price$ or pricing).ti,ab,kw.	477682
55	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).ti,ab,kw.	179278
56	((patient$ or caregiver$ or carer$ or social$ or society$ or family$ or work$) adj2 (burden$ or productiv$)).ti,ab,kw.	43349

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.	486456
58	(absenteeism or presenteeism or employment or unemployment).ti,ab,kw. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	176223
59	or/38-58	1827746
60	("conference abstract" or "conference review").pt.	4536774
61	limit 60 to yr="1974-2020"	4126125
62	exp animals/ not exp humans/	4993925
63	(comment or editorial).pt.	737789
64	historical article/	1
65	or/61-64	9464443
66	4 and (10 or 37 or 59)	810
67	66 not 65	553
68	limit 67 to yr="2021 -Current"	169

Table 72. Search terms used in Cochrane Database of Systematic Reviews Issue 9 of 12, September 2022, Cochrane Central Register of Controlled Trials, Issue 8 of 12, August 2022 (searched via Cochrane Library Wiley Online on 7th September 2022)

#	Searches	Results
#	searches	results
#1	[mh “neurofibromatosis 1”]	65
#2	("1" or i or peripheral or von Recklinghausen) near/2 neurofibroma*:ti,ab,kw	138
#3	(NF1 or NFI or NF-1 or NF-I):ti,ab,kw	276
#4	#1 or #2 or #3	309
#5	[mh ^“neurofibroma”] OR [mh ^“neurofibroma, Plexiform”]	51
#6	(plexiform neurofibroma* or plexiform neuroma*):ti,ab,kw	21
#7	#5 or #6	66
#8	#4 and #7 (with Cochrane Library publication date from Jan 2021 to Oct 2022)	13

Table 73. Search terms used in INAHTA (https://database.inahta.org/) (searched 7th September 2022)

#	Searches	Results
1	(Neurofibromatosis 1 [mh] or (((“neurofibroma* 1”) or (“neurofibroma* i”) or (“peripheral neurofibroma*”) or (“von Recklinghausen”))) or ((NF1	0

or NFI or NF-1 or NF-I)) FROM 2021 TO 2022

Table 74. Search terms used in Econlit (searched via Ovid SP on 7th September 2022)

#	Searches	Results
1	neurofibromatosis.mp.	0
2	Recklinghausen.mp.	0
3	NF1.mp.	0
4	NF-1.mp.	0

Figure 36. PRISMA flow diagram for HRQoL SLR (September 2022)

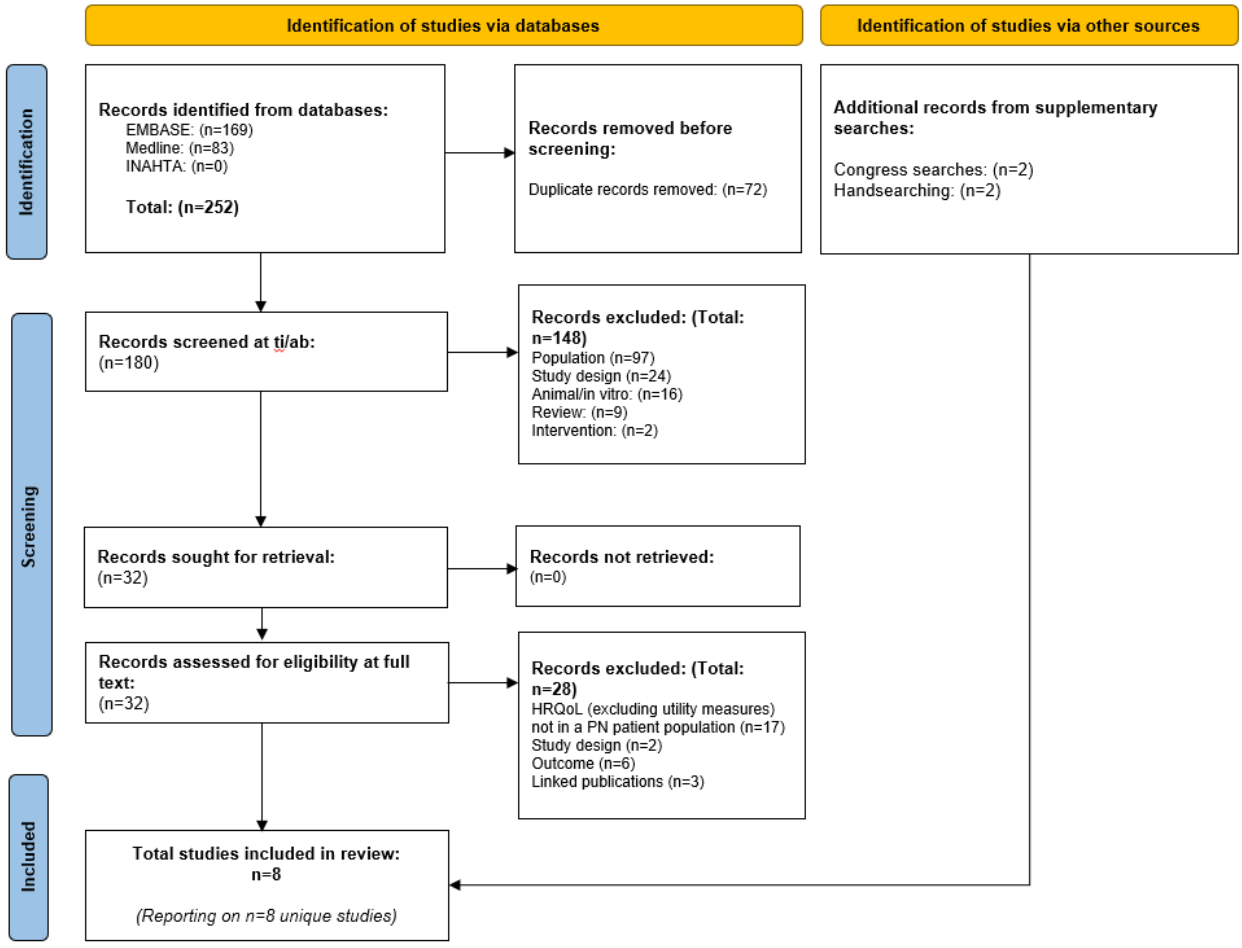


Table 75. Summary of HRQoL studies included in the SLR

<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
[116-118]

SPRINT: Phase II, Stratum 1</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></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>Domain</th><th>Mean (range)</th><th></th><th>Mean (9 CI) diffe (n=29)</th></tr><tr><th></th><th>Baseline (n=33)</th><th>12 months (n=29)</th><th></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</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</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</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, 1</td></tr></table></td><td>Consistency with DMC reference case: HRQoL values are reported rather than utility values, which deviates from the DMC preference.

The study took place in the US, which may</td><td></td></tr>
</table>

Age (years)	
Median	10.2
Range	3.5–17.4
Target NF volume (mL)	
Median	487
Range	5–3820
NF progression status at entry (n)	
Progressive	21
Nonprogressive	15
Insufficient data	14
NF-related complications,* n (%)	
Disfigurement	44(88)
Motor dysfunction	33(66)

then annually to 4 years (cycle 48)

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.

School*	66.3 (10.0–100.0)	70.6 (0–100.0)	5.0 (-2.2, 12.2)

**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

Domain	Mean (range)		Mean (S CI) diffe (n=45)
	Baseline (n=50)	12 months (n=45)	
Total	60.8 (20.7–98.9)	73.3 (39.1–98.9)	13.0 (8.1,17
Physical	60.6 (9.4–100.0)	73.2 (18.8–100.0)	13.8 (7.8,19
Emotional	64.9 (15.0–100.0)	82.2 (40.0–100.0)	17.4 (1 23.8)
Social	57.9 (10.0–100.0)	69.7 (20.0–100.0)	11.7 (5.0,18

not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Patients included were paediatric and had NF1 with inoperable, and progressive PNs aligned with the decision problem. However, it was unclear if PN were symptomati

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.

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% 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)*

c, which deviates from the decision problem.

*** 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

Domain	Mean (range)		Mean (95% difference
	Baseline	12 months	
Mobility*	37.4 (19.8–56.5)	41.1 (21.1–56.5)	3.0 (1.3, 4.7)
Upper Extremity**	38.1 (14.0–54.8)	40.6 (14.0–54.8)	1.8 (-0.7, 4.4)

**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*

Data from 4 year follow up (cycle 48):

- From baseline to cycle 48, child ratings (n=19 with both scores) of worst pain in the past week for their physician-selected target tumour (p=0.016; median change of -2.0) and child (n=18) and parent (n=24) mean ratings of pain interference improved significantly (both p<0.01), with declines starting as early as cycle 4.

- Of the 10 children (of n=19) with baseline tumour pain intensity scores of ≥2 points, all reported clinically meaningful decreases of ≥2 points at cycle 48; of these, 7 had a volumetric partial response (70%).

- Parent (n=25) mean total QoL scores, and mean physical, emotional, and social domain scores improved significantly (p<0.01) and child (n=19) mean total QoL and emotional domain

scores were significantly improved (p<0.05) at cycle 48.

- Parent (n=29) and child (n=21) GIC ratings at cycle 36 both indicated 'much improved' change in tumour pain and in other tumour-related problems.

Gross 2022 [119] **SPRINT: Phase II, Stratum 2**	Patients Children with a clinical diagnosis of NF1, 2-18 years of age, able to swallow intact capsules, and with inoperable measurable PN. [Patients enrolled on Stratum 2 of SPRINT were those with no clinically significant PN-related morbidity but potential for development of significant PN-related morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, paraspinal lesions that could cause myelopathy, brachial or lumbar plexus lesions that	USA	Data from 25 children with NF1 PN were analysed. Tumour response evaluation was performed centrally by volumetric analysis of the MRI of the target PN.	HRQL reported for patients with NF1 and PN. HRQoL was assessed at baseline and after 12 months of treatment of selumetinib (pre-cycle 13).	Children ≥8 years completed the NRS-11, the PII, the PedsQL and the GIC scale. Parents of children ≥5 years old completed the parent-report PII and GIC scale and parents of children ≥2 years old completed the parent-report PedsQL	**Table 1. Pain intensity: self-reported NRS-11 scores** **Timepoint** / **Mean (range)** / **Mean difference (95% CI), p value** Baseline (n=18) / 1.33 (0–6) / Pre-cycle 13 - baseline: -1.00 (-1.87, -0.13), p=0.016 Pre-cycle 13 (n=16) / 0.38 (0–3) / ***Abbreviations:*** *CI: confidence interval; NRS, numeric rating scale* **Table 2. Pain interference Index (PII): self-and parent-report scores** **Timepoint** / **Mean (range)** / **Mean difference (95% CI), p value**	**Consistency with DMCreference case:** HRQoL values are reported rather than utility values, which deviates from the DMC preference. The study took place in the US, which may

could cause nerve compression and loss of function, lesions that could result in major deformity (eg, orbital lesions) or become significantly disfiguring, lesions of the extremity that could cause limb hypertrophy or loss of function, and lesions that could become painful]

Population characteristics (n=50)

Disease characteristics	Data
Median baseline tumour volume, mL (range) [IQR]	381 (12–3,159) [140–740]
Progressive PN growth at baseline, n	11
Functional evaluations within normal limits[b]	

Baseline		Pre-cycle 13 - baseline: *Self (n=15):* -0.32 (-10.76, 0.11), p=0.12 *Parent (n=20):* -0.30 (-0.77, 0.17), p=0.28
Self (n=18)	0.68 (0–2.33)	
Parent (n=24)	0.47 (0–3.5)	
Pre-cycle 13		
Self (n=15)	0.48 (0–1.67)	
Parent (n=20)	0.21 (0–1.67)	

Abbreviations: *CI: confidence interval*

Table 3. PROMIS Physical Function scores

not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Patients included were paediatric and had NF1 with inoperable, and progressive PNs aligned with the decision problem. However, it was unclear if PN were symptomati

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, n (%)	16 (64)
Number of potential PN morbidities per subject, median (range)	3 (1–5)
Race	
White	17 (68)
Black or African American	4 (16)

Domain	Mean (range)	Mean difference (95% CI), p value
Mobility		
Baseline		Pre-cycle 13 - baseline: *Self (n=10): 3.*2 (-1.5, 7.9), p=0.20 *Parent (n=14):* 2.5 (-1.0, 6.0), p=0.29
Self (n=12)	47.0 (35.6–58.5)	
Parent (n=16)	43.9 (32.7–56.5)	
Pre-cycle 13		
Self (n=12)	49.1 (38.6–58.5)	

c, which deviates from the decision problem.

Asian	3 (12)
Unknown	1 (4)
Target PN location, n (%)	
Head only	4 (16)
Head/neck	4 (16)
Neck/trunk	4 (16)
Trunk only	9 (36)
Trunk/extremity	4 (16)
Extremity only	0 (0)
Target PN progression status, n	
Progressive	11
Non-progressive	9
Unknown	5
Target PN type, n (%)	
Typical PN	20 (80)

Parent (n=16)	44.4 (28.6– 56.5)	
Upper extremity		
Baseline		Pre-cycle 13 - baseline: *Self (n=11): 3.1* (0.0, 6.1), p=0.062 *Parent (n=13):* 3.6 (0.04, 7.1), p=0.074
Self (n=12)	49.3 (35.9–56.7)	
Parent (n=15)	42.0 (28.2–54.8)	
Pre-cycle 13		
Self (n=13)	52.5 (36.9–56.7)	

Nodular PN	4 (16)
Solitary nodular PN	1 (4)
Type of potential PN-related morbidity, n (%)	
Motor	17 (68)
Disfigurement	17 (68)
Pain/sensory deficit	15 (60)
Bowel/bladder	12 (48)
Airway	7 (28)
Vision	3 (12)
Other (e.g. facial muscle dysfunction, hearing loss, abnormal speech or swallowing)	7 (28)

[a]≥20% increase in PN volume within 15 months prior to enrolment [b]Excluding patients with non-PN related

Parent (n=16)	44.3 (27.5–54.8)

Abbreviations: *CI: confidence interval; PROMIS: Patient-Reported Outcomes Measurement Information System*

Table 4. PedsQL generic QOL Scale scores

Domain	Mean (range)	Mean difference (95% CI), p value
Total		
Baseline		Pre-cycle 13 - baseline: *Self (n=16): 5.6* (1.0, 10.2), p=0.029 *Parent (n=21):* 4.1 (-1.4, 9.5), p=0.087
Self (n=18)	82.0 (58.7–100.0)	

comorbidities limiting their functional status (e.g. scoliosis)

Abbreviations: *IQR: inter-quartile range; PN: plexiform neurofibroma; ROM: range of motion.*

Intervention
Selumetinib,
25 mg/m2, every 12 hours, 28 day cycles on a continuous dosing schedule.

Comparator
None.

Recruitment
Patients were recruited from four participating hospitals in the USA between 12th November 2015 and 6th September 2018.

Parent (n=25)	80.2 (54.2–100.0)	
Pre-cycle 13		
Self (n=16)	87.5 (62.0–100.0)	
Parent (n=21)	83.3 (52.2– 100.0)	
Physical		
Baseline		Pre-cycle 13 - baseline: *Self (n=16): 3.3* (-3.9, 10.6), p=0.43 *Parent (n=21):* 4.8 (-3.3, 12.8), p=0.13
Self (n=18)	83.2 (43.8–100.0)	

Parent (n=25)	82.7 (40.6–100.0)	
Pre-cycle 13		
Self (n=16)	85.7 (59.4–100.0)	
Parent (n=21)	84.8 (31.3–100.0)	
Emotional		
Baseline		Pre-cycle 13 - baseline: *Self (n=16): 6.2* (0.4, 12.1), p=0.055 *Parent (n=21):* 2.9 (-3.0, 8.7), p=0.33
Self (n=12)	85.6 (40.0–100.0)	

Parent (n=15)	82.6 (30.0–100.0)	
Pre-cycle 13		
Self (n=12)	91.9 (60.0–100.0)	
Parent (n=15)	85.7 (50.0–100.0)	
Social		
Baseline		Pre-cycle 13 - baseline: *Self (n=16): 5.9* (-0.2, 12.0), p=0.043 *Parent (n=21):* 5.7 (-3.2, 14.7), p=0.15
Self (n=12)	80.8 (40.0–100.0)	

Parent (n=15)	79.9 (31.3–100.0)	
Pre-cycle 13		
Self (n=12)	87.2 (50.0–100.0)	
Parent (n=15)	85.5 (45.0–100.0)	
School		
Baseline		Pre-cycle 13 - baseline: *Self (n=12): 9.6* (3.5, 15.7), p=0.0039 *Parent (n=16):* 7.1 (-5.7, 19.9), p=0.13
Self (n=14)	78.6 (45.0–100.0)	

						Parent (n=20) 73.6 (45.0–100.0)	
						Pre-cycle 13	
						Self (n=16) 86.3 (55.0–100.0)	
						Parent (n=21) 76.4 (25.0–100.0)	
						Abbreviations: *CI: confidence interval;*	
Hamoy-Jimenez 2020 [120, 121]	Patients All adult patients met the clinical diagnostic criteria for NF1 and/or had genetically confirmed NF1. Population characteristics **Characteristic / Value: Total / Male / Female** Female 57% NA NA Male 43% NA NA	Canada, academic clinic.	N=162 Response rate not reported.	Not Reported.	HSUV were assessed using the EQ-5D-5L. A Canadian valuation algorithm was used to estimate utility scores [122]. The study was cross-sectional; therefore, patients were assessed at	Mean (SD) EQ-5D-5L utility score • Total population (n=162), 0.73 (0.24) • Female (n=92), 0.72 (0.25) • Male (n=70), 0.75 (0.24), p=0.41 vs female	**Consistency with DMC reference case:** Health utility values were elicited using the EQ-5D-5L, in line with the DMC preference. The study took place in Canada,

Mean age (SD)	33 (13.5)	35 (15)	32 (12)
Known PN	39%	31%	45%
History of MPNST	9%	8%	9%
Optic glioma	15%	13%	17%
Ablon's index	Median, 2 (range 1–3)	Mean, 1.74 (SD 0.73)	Mean, 1.67 (0.669)

***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.

one timepoint only.

and valued utilities using a Canadian value set, which may not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: The study included patients with NF1, relevant to the decision problem.

However, not all

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>patients had PN, and it was unclear if PN were inoperable and symptomatic, which deviates from the decision problem.</td>
</tr>
<tr>
<td>Lai 2019 [123]</td>
<td>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
<table>
<tr><th>Characteristic</th><th>Value</th></tr>
<tr><td>Mean age (SD)(years)</td><td>12.53 (2.7)</td></tr>
</table>
</td>
<td>US</td>
<td>Data from 140 children with NF1 PN were analysed.

Response rate is not reported.</td>
<td>HRQoL reported for total patient population, all had NF1 with PN.

HRQoL for adverse events were not reported.</td>
<td>HRQoL was assessed using PROMIS, which was completed by the patient.

HRQoL was also assessed using the NeuroQoL questionnaire.</td>
<td>Table 2. PROMIS scores reported by patient
<table>
<tr><th>Domain</th><th>Mean (SD)</th><th>95% CI</th></tr>
<tr><td>Anxiety</td><td>53.2 (12.2)</td><td>51.2–55</td></tr>
<tr><td>Depressive symptoms</td><td>53.5 (12.2)</td><td>51.5–55</td></tr>
<tr><td>Fatigue</td><td>50.2 (14.0)</td><td>47.9–52</td></tr>
<tr><td>Meaning and purpose</td><td>40.1 (7.7)</td><td>38.7–41</td></tr>
<tr><td>Mobility</td><td>40.9 (9.8)</td><td>39.2–42</td></tr>
</table>
</td>
<td>Consistency with DMC reference case: HRQoL values are reported rather than utility values, which deviates from the DMC preference.</td>
</tr>
</table>

Female (%)	35.71
Male (%)	64.29
White (%)	64.29
Black/African American	30.00
Age at diagnosis (years)	
<5	57.14
5–9	26.43
10–17	16.43
Café-au-lait spots	
No	0.71
≤6	12.86
6–20	48.57
>20	37.86
pNFs	

Pain interference	49.8 (13.4)	47.5–52.0
Peer relationship	43.0 (9.1)	41.5–44.6
Positive affect and well-being	46.4 (7.6)	45.1–47.7
Psychological stress response	56.8 (9.8)	55.1–58.5
Upper extremity function	39.7 (12.4)	37.6–41.9

***Abbreviations**: CI: confidence interval; PROMIS: Patient-Reported Outcomes Measurement Information System; SD: standard deviation*

NeuroQoL
Mean (SD) stigma score 53.3 (8.0).

The study took place in the US, which may not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Patients included were paediatric and had NF1 with inoperable and progressive PNs, aligned with the decision problem.

No	4.29
1	39.29
1–5	42.86
≥5	6.43
Don't know/unsure	7.15
Chronic itching	
No	58.57
Yes	38.57*
Unsure	2.86
Pain	
No	32.86
Yes	67.14

**37.04% received treatment for chronic itching*
***Abbreviations**: pNF: neurofibromatosis type 1-related plexiform*

However, both symptomatic and asymptomatic patients were included which does not align with the decision problem.

neurofibromas; SD: standard deviation

Recruitment
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

Lo 2021 [124]	Participants Vignettes were developed for a range of NF1-PN health states for evaluation in	UK	100 TTO interviews were conducted	An overview of the nine health	TTO was used to estimate HSUVs using vignette; vignettes were	**Table 1. VAS ratings for health state vignettes (N=100)** **Mean (SD) 95% CI**	**Consistency with DMCreference case:** Health

general public interviews using the TTO method. Nine vignettes were developed, varying by child/ adult status, treatment status, and PN location

Health states	Patient profile	
	Treatment and disease status	PN location
Cu-Tx	Untreated, progressed	Unspecified
CF-Tx		Face
CT-Tx		Trunk
CL-Tx		Leg
AU-Tx	Untreated, stable	Unspecified
CU+Tx	Treated, improved	
CF+Tx		Face

Feedback on the vignettes was sought from patients (n=8), caregivers (n=6) and clinical experts (n=4).

states is provided in the table.

developed in line with the NICE Task and finish group recommendations for generating utility estimates for health states using vignettes when EQ-5D data are unavailable [125].

CU-Tx	43.7 (20.5)	39.6–47.8
CF-Tx	35.0 (20.7)	30.9–39.1
CT-Tx	42.7 (19.3)	38.9–46.5
CL-Tx	43.8 (19.8)	39.9–47.7
AU-Tx	53.3 (19.0)	49.5–57.0
CU+Tx	63.2 (17.8)	59.7–66.7
CF+Tx	51.7 (19.9)	47.7–55.6
CT+Tx	61.2 (16.3)	58.0–64.4
CL+Tx	61.7 (16.8)	58.3–65.0

***Abbreviations**: CI: confidence interval; SD: standard deviation; VAS: visual analogue scale*

Table 12. TTO ratings for health state vignettes (N=100)

	Mean (SD)	95% CI
CU-Tx	0.510 (0.365)	0.438–0.583

utility values were elicited using the TTO, which deviates from the DMC preference (EQ-5D-5L).

The model used utilities from health state vignettes which were modelled from the general population using TTO – the validity of the obtained utilities was dependent on the health state

CT+Tx		Trunk
CL+Tx		Leg

***Abbreviations**: C: child state; A: adult state; U: unspecified; F: face; T: trunk; L: leg: -Tx: untreated; +Tx: treated*

Recruitment

A total of 100 TTO were conducted with a sample of participants that were broadly representative of the UK general population in terms of age, sex, and ethnicity.

Patient characteristics

Characteristic	UK sample for TTO valuation	UK population [a]
Age, years	Mean (SD),	Median, 39.4

CF-Tx	0.358 (0.407)	0.277–0.438
CT-Tx	0.483 (0.378)	0.408–0.558
CL-Tx	0.506 (0.381)	0.430–0.582
AU-Tx	0.615 (0.318)	0.552–0.678
CU+Tx	0.740 (0.203)	0.700–0.780
CF+Tx	0.581 (0.290)	0.523–0.639
CT+Tx	0.725 (0.186)	0.688–0.761
CL+Tx	0.739 (0.192)	0.701–0.777

***Abbreviations**: CI: confidence interval; SD: standard deviation; TTO: time trade off*

vignettes that were used to elicit utilities

The study took place in the UK, and therefore data might not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: The study included patients with NF1,

	42.0 (16.4)	
Sex, n (%)		
Male	49 (49)	(49)
Female	51 (51)	(51)
Ethnicity, n (%)		
White	80 (80)	(86)
Asian	6 (6)	(8)
Black	5 (5)	(3)
Mixed	8 (8)	(2)
Other	1 (1)	(1)

Footnote: *[a]Figures based on data from the 2011 UK national census*
Abbreviations*: SD: standard deviation; TTO: time trade off*

relevant to the decision problem.

Ren 2020 [126]

Patients

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.

Population characteristics

Characteristic	Value
Age range (years)	3–49
Craniofacial PN (n)	15

China

N=27

Response rate is not reported.

HRQoL for NF1 patients with craniofacial or non-craniofacial PNs was reported.

HRQoL was measured using the INF1-QOL questionnaire.

Table 1. Total INF1-QOL Scores

	Mean	SD	95%CI	Median
Total score craniofacial patients	6.47	3.8	4.34–8.59	6
Total score non-craniofacial patients	6.42	3.4	4.26–8.57	6

***Abbreviations**: CI: confidence interval; INF1-QOL: Impact of NF1 on Quality of Life; SD: standard deviation*

Table 2. Single item scores INF1-QOL

Item	No problem, n (%)	Mild problem, n (%)	Moderate problem, n (%)	Se pro n (
Vision	17 (63.0)	7 (25.9)	3 (11.1)	0 (
Cosmetic appearance	8 (29.6)	12 (44.4)	5 (18.5)	2 (
Pain quality	12 (44.4)	11 (40.7)	4 (14.8)	0 (

Consistency with DMC reference case: HRQoL values are reported rather than utility values, which deviates from the DMC preference.

The study took place in China, which may not be directly relevant to clinical practice in Denmark.

Non-craniofacial PN	12
Mean age craniofacial patients (years)	20.0
Mean age non-craniofacial patients (years)	23.0
Male craniofacial patients (n, %)	6, 40.0
Male non-craniofacial patients (n, %)	3, 25.0
Female craniofacial patients (n, %)	9, 60.0
Female non-craniofacial patients (n, %)	9, 75.0
cNFs ≥50 craniofacial patients (n, %)[a]	7, 46.7
cNFs <50 craniofacial patients (n, %) [a]	8, 53.3

Pain intensity	11 (40.7)	9 (33.3)	5 (18.5)	2 (7.4)
Learning problems	17 (63.0)	8 (29.6)	2 (7.4)	0 (0)
Behaviour and personality	22 (81.5)	4 (14.8)	1 (3.7)	0 (0)
Mobility and walking	15 (55.6)	10 (37.0)	2 (2.7)	0 (0)
Weakness, numbness, clumsiness in hands	22 (81.5)	5 (18.5)	0 (0)	0 (0)
Speech	22 (81.5)	5 (18.5)	0 (0)	0 (0)
Bones	17 (63.0)	9 (33.3)	1 (3.7)	0 (0)
Breathing	24 (88.9)	3 (11.1)	0 (0)	0 (0)
Sleeping	22 (81.5)	5 (18.5)	0 (0)	0 (0)

Relevance to the decision problem: Patients included were NF1 patients with PN, so is aligned to the decision problem; however this study included adults and children, limiting its applicability. It is also unclear whether all PNs are inoperable and symptomatic, which may further

cNFs ≥50 non-craniofacial patients (n, %) [a]	3, 25.0
cNFs <50 non-craniofacial patients (n, %) [a]	9, 75.0
Familial inheritance craniofacial patients (n,%)	8, 53.3
Sporadic inheritance craniofacial patients (n,%)	7, 46.7
Familial inheritance non-craniofacial patients (n,%)	4, 33.3
Sporadic inheritance non-craniofacial patients (n,%)	8, 66.7
With other complications craniofacial patients (n,%)[b]	9, 60.0

Role and outlook on life	16 (59.3)	3 (11.1)	7 (25.9)	1 (3.7) limit relevance to the decision problem.
Depression and anxiety	21 (77.8)	4 (14.8)	2 (7.4)	0 (0)

***Abbreviations**: INF1-QOL: Impact of NF1 on Quality of Life Questionnaire*

Without other complications craniofacial patients (n,%)[b]	6, 40.0
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 [127]	Patients NF1 patients with symptomatic and inoperable PNs, aged >16 years. Population characteristics **Characteristic / Value** Males (n) 20 Females (n) 18 Median age (years) 23 Age range (years) 16–39	US	38 patients. Response rate not reported.	HRQoL reported for whole population, all had NF1 with inoperable PN. HRQoL for specific health states or adverse events not reported.	HRQoL was assessed using the NF1 PedsQL. HRQoL was assessed at one timepoint, before receiving treatment.	**NF1 PedsQL, mean total functioning score (SD):** 68.1 (19.6).	**Consistency with DMC reference case:** HRQoL values are reported rather than utility values, which deviates from the NICE preference. The study took place in the US, which may

Tumour visibility, mild (%)*	40
Tumour visibility, moderate (%)*	47
Tumour visibility, severe (%)*	13
NF1 symptoms, mild (%)*	26
NF1 symptoms, moderate (%)*	50
NF1 symptoms, severe (%)*	24

**Patients rated own disease visibility and symptom severity on a scale of mild, moderate, or severe*
***Abbreviations**: NF1: neurofibromatosis type 1*

Recruitment
This patient population is from two clinical trials (NCT02101736 and

not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Patients included were NF1 patients with inoperable and symptomatic PN, so is aligned to the decision problem; however the study included adults as well as

	NCT02096471) before receiving treatment. Details of recruitment are not reported.						children, limiting the applicability to the decision problem.
Weiss 2014 (NCT00634270) [128]	Patients 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. Population characteristics	US	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).	HRQoL was reported for the patient population, all had NF1 with an unresectable PN. HRQoL for adverse events were not reported.	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	PedsQL 4.0 **Table 1.Total scores, child reported (n=6)** **Baseline** **60.15** Course six 71.56 Mean change 11.41* **p=0.14* **Table 2. Emotional domain scores, child reported (n=6)** **Baseline** **55.83** Six months 74.17 Mean change 18.33	**Consistency with DMC reference case:** HRQoL values are reported rather than utility values, which deviates from the DMC preference. The study took place in the US, which may not be

Characteristic	Value
Female, n (%)	5 (38.5)
Male, n (%)	8 (61.5)
Age (years)	
Mean (range)	16 (3–35)
Race	
White, n (%)	10 (76.9)
Black/ African American, n (%)	2 (15.4)
Asian, n (%)	1 (7.7)

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.

The parents of the children also reported on their child's QoL.

courses of sirolimus therapy.

*p=0.0354

Table 3."School" domain scores, child reported (n=6)

Baseline	**52.50**
Six months	69.17
Mean change	16.67

*p=0.0055

Table 4. Physical domain scores, child reported (n=6)

Baseline	**68.75**
Six months	79.17
Mean change	10.42

*p=0.2545

Table 5. Social domain scores, child reported (n=6)

Baseline	**58.33**

directly relevant to clinical practice in Denmark.

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 completely

	Recruitment Patients were enrolled at one of nine Department of Defence funded NF Clinical Consortium sites.					Six months 59.17 Mean change 0.83 **p=0.9669* **Table 6. Total scores, parent proxy (n=6)** **Baseline 63.10** Course six 61.23 Mean change -1.88* **p=0.5108* FACT-G (adults only) Change in mean scores from baseline to course six (45.33 to 41.47; p=0.2264).	aligned to the decision problem, but some outcomes are reported separately for these two groups.
Weiss 2021 (NCT02096471) [129]	Patients Subjects aged ≥16 years with symptomatic or growing, inoperable PNs Key eligibility criteria: Patients aged ≥16 years with NF1 (using NIH Consensus Conference criteria) and an	US	A total of 19 patients with NF1 and PN were enrolled between July 2014 and	HRQoL reported for total patient population, all had NF1 with PN.	NRS-11, BPI Interference subscale, and PedsQL NF1 module were completed	**Table 1. NRS-11 (worst tumour pain) scores for patients with NF1-PN** **Item / Mean (SD)** *PR* Course 0 (n=8) 5.1 (3.1)	**Consistency with DMC reference case:** HRQoL values are reported rather than utility

unresectable PN either with significant progression in the past year (defined as ≥20% increase in the volume, ≥13% increase in the product of the two longest perpendicular diameters, or ≥ 6% increase in the longest diameter) or with PN-related significant morbidity; PNs were at least 3 mL and amenable to volumetric MRI analysis; Karnofsky ≥50%

Population characteristics

Characteristics	Data
Age, years mean (SD) [median, range]	24.6 (6.9) [24, 16-39]
Sex, n (%)	
Male	11 (57.9)
Race, n (%)	
Caucasian	8 (42.1)

September 2015.

All 19 patients completed the PRO measures at baseline, 18 at course 4, 15 at course 8, and nine at course 12.

HRQoL was assessed at enrolment and after courses 4, 8, and 12, and then after courses 18 and 24 for those who continued therapy.

Course 4 (n=8)	3.3 (2.8)
Course 8 (n=8)	3.8 (3.2)
Course 12 (n=8)	2.7 (3.4)
No PR	
Course 0 (n=11)	4.8 (3.8)
Course 4 (n=10)	2.9 (3.3)
Course 8 (n=7)	3.0 (2.8)
Course 12 (n=1)	2.0 (N/A)

***Abbreviations**: N/A: not applicable; NRS: numerical rating scale; PR: partial response; SD: standard deviation*

Table 2. BPI (pain interference) scores for patients with NF1-PN

Item	Mean (SD)
PR	
Course 0 (n=8)	3.3 (2.9)

values, which deviates from the DMC preference.

The study took place in the US, which may not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Patients included paediatric and adult patients with NF1

Black or African American	4 (21.1)
Native Hawaiian or other Pacific Islander	0 (0)
Asian	2 (10.5)
American Indian or Alaska Native	0 (0)
Others	4 (21.1)
Unknown	1 (5.2)
Ethnicity, n (%)	
Hispanic or Latino	3 915.8)
Non-Hispanic or non-Latino	13 (68.4)
Unknown	3 (15.8)

Abbreviations: *SD: standard deviation*

Course 4 (n=8)	2.8 (2.8)
Course 8 (n=8)	1.7 (2.4)
Course 12 (n=8)	2.0 (2.5)
No PR	
Course 0 (n=11)	2.4 (2.7)
Course 4 (n=10)	2.0 (2.9)
Course 8 (n=7)	2.1 (2.6)
Course 12 (n=1)	4.0 (N/A)

Abbreviations*: BPI: Brief Pain Interference; N/A: not applicable; PR: partial response; SD: standard deviation*

Table 3. PedsQL-NF1 (total functioning) scores for patients with NF1-PN

Item	Mean (SD)
PR	
Course 0 (n=8)	62.9 (20.8)

and symptomatic or growing, inoperable PNs, aligned with the decision problem.

Intervention
Mirdametinib 2 mg/m2/dose orally BID (maximum dose of 4 mg BID; capsules swallowed whole) in a 3-week on/1-week off sequence. Patients could receive a maximum of 24 four-week courses

Recruitment
Patients were enrolled at NF Clinical Trials Consortium sites

Course 4 (n=8)	67.7 (19.2)
Course 8 (n=8)	73.7 (22.2)
Course 12 (n=8)	66.7 (20.5)
No PR	
Course 0 (n=11)	68.1 (20.1)
Course 4 (n=10)	73.1 (16.8)
Course 8 (n=7)	69.2 (16.6)
Course 12 (n=1)	75.7 (N/A)

***Abbreviations**: N/A: not applicable; NRS: numerical rating scale; PR: partial response; SD: standard deviation*

Widemann 2014 (NCT00021541) [77]	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.	US	A total of 60 patients with NF1 and PN. 31 and 29 patients were	HRQOL reported for patient population, all had NF1 with inoperable PN.	IPI Scale Parent total scores for participants on placebo were compared with scores for	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).	**Consistency with DMC reference case:** HRQoL values are reported rather than

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. <u>Population characteristics</u> **Characteristic Placebo Tipifarr**	randomised to receive tipifarnib and placebo, respectively. Response rate was not reported, HRQoL data was given for 35 patients at baseline (tipifarnib n=17, placebo n=18) and 28 pre-cycle ten (tipifarnib n=16, placebo n=12). 35 patients' parents	HRQoL was reported at baseline, pre-cycle four, seven, and ten, and then after every six cycles. HRQoL for adverse events were not reported.	participants receiving tipifarnib	**Placebo (n=18):** Mean score: 3.68 (p vs. baseline=0.66). Mean emotional functioning domain score: 3.64 (p vs. baseline=0.99). <u>IPI score: pre-cycle ten</u> **Tipifarnib (n=16):** Mean score: 3.84 (p vs. baseline=0.03). **Placebo (n=12):** Mean score: 3.84 (p vs. baseline=0.11).	utility values, which deviates from the DMC preference. The study took place in the US, which may not be directly relevant to clinical practice in Denmark. **Relevance to the decision problem:** Patients included were NF1 patients with

Median age (years)	8.2	9.7	(placebo n=18, tipifarnib (n=17) responded to the HRQOL questionnaire.	inoperable PN who had received tipifarnib or placebo, so is aligned to the decision problem; however, the study included adults and paediatric patients, and is unclear whether PN is symptomatic, limiting the applicability to the decision problem.
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: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; PNs: Plexiform neurofibromas*

Intervention
Tipifarnib, 200 mg/m2 orally every 12 h, for 21 days followed by seven days' rest.

Placebo, same regimen as intervention.

Recruitment

Clinical trial (NCT00021541) included ten participating sites, of which seven enrolled participants.

Wolkenstein 2009 [130]

Patients
Records from families with at least one child aged between eight and 16 years.

Population characteristics

Characteristic	Value
Male/female ratio	1:1
Mean age (years), ± SD	12.1 ± 2.6
More than 2 PNs (n=76), n (%)	5 (7)
Orthopaedic manifestations, n (%)	26 (33)

France

140 families were contacted, and 79 (56%) returned the questionnaires.
CDLQI questionnaire scores were available from 75 children, of whom five had NF1 with PN.

HRQoL was assessed for NF1 patients with and without PN.
Results from patients with PN are presented here.

HRQoL for specific adverse events are not reported.

HRQoL was assessed using the French version of the CDLQI.

Table 2. CDLQI scores for patients with PN (n=5)

Dimension	Score	Impairment compared to patients with PNs (n=68)
Symptoms and feelings, mean (SD)*	26.7 (11.3)	p=0.005
School or holidays, mean (SD)[a]	20.0 (13.3)	p=0.007

[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*

Consistency with DMC reference case:
HRQoL values are reported rather than utility values, which deviates from the DMC preference.

The study took place in France, which may not be directly relevant to

Dysmorphic features, n (%)	14 (18)
Hydrocephalus, n (%)	3 (4)
Learning difficulties, n (%)	54 (68)
Optic pathway glioma (n=64), n (%)	18 (28)
CDLQI score, mean ± SD**	3.4 ± 3.0 (11.3 ± 10.1)

***Abbreviations**: CDLQI: Children's Dermatology Life Quality Index; PN: plexiform neurofibroma; SD: standard deviation*

Recruitment
Recruitment occurred via mail in November 2005.

clinical practice in Denmark.

Relevance to the decision problem: The patients considered have NF1 and PN and are paediatric patients, so are relevant to the decision problem. It is unclear whether the PNs are inoperable and symptomatic, which may be a

limit relevance to the decision problem.

Wolters 2015 [57]

Patients
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.

Population characteristics

Characteristic	Value (all included)	Value (Adolescent patients

US

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).

HRQoL reported for the patient population, all of which had NF1 PN.

HRQoL for specific adverse events are not reported.

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.

Table 1. Patient HRQOL scores measured by IPI

Population (N=40)	Mean (range [SD])
Caregiver rating	68.7 (45.7–92.1 [1
Adolescent self-report	68.4 (48.0–87.5 [1
Moderate/severe disease, caregiver	64.2
Mild disease, caregiver	79.2
Moderate/severe disease, self-report	65.3
Mild disease, self-report	74.8

Consistency with DMCreference case:
HRQoL values are reported rather than utility values, which deviates from the DMC preference.

The study took place in the US, which may not be directly relevant to clinical

	patients) N=60	[10—18 years]) N=42
Female, n (%)	21 (35%)	15 (36%)
Mean age, years (SD)	12.7 (3.6)	14.5 (2.4)
Age range	6.3–18.8	10.6–18.8
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*

***Abbreviations**: HRQOL: health related quality of life; IPI: Impact of Pediatric Illness form; SD: standard deviation*

practice in Denmark.

Relevance to the decision problem: Patients included have NF1 PN and are a paediatric population, so are relevant to the decision problem. Symptom severity varied so full population might not align with the decision problem. Also unclear whether the

PN is inoperable, which may limit relevance to the decision problem.

Yang 2022 [131]

Patients/caregivers

Paediatric patients aged 8–18 years with NF1-PN and their caregivers, as well as caregivers of patients aged 2–7 years with NF1-PN

Pediatric patients were eligible to participate in the survey if they met the age requirement (aged 8–18 years), were naive or new to selumetinib treatment (defined as ≤ 1 month of use), residents of the US, and able to read and write English. Caregivers for all patients with NF1-PN (aged

USA

Sixty-one patients and 82 caregivers responded to the survey

HRQoL reported for the patient population, all of which had NF1 PN.

HRQoL was assessed using the PedsQL and EQ-5D-Y

Physical functioning was assessed using the PROMIS subscales for mobility and upper extremity functioning.

NRS-11 was used to assess pain and PII was used to assess the

Table 1. PedsQL acute version scores

Item	Mean (SD)	Median (range)
Child self-reported response (N=61)		
Physical functioning	63.7 (25.1)	65.6 (0.0, 100.0)
Emotional functioning	56.1 (20.0)	55.0 (10.0, 100.0)
Social functioning	60.7 (22.6)	65.0 (0.0, 100.0)
School functioning	50.3 (22.9)	50.0 (5.0, 100.0)
Total	58.5 (19.3)	62.0 (15.2, 96.7)

Consistency with DMC reference case: HRQoL values are reported rather than utility values, which deviates from the DMC preference.

The study took place in the US, which may not be

2–18 years) were required to be aged 18 or older, residents of
the US, and able to read and write English.

Population characteristics of paediatric patients (N=82)

Characteristic	Value
Female, n (%)	44 (53.7%)
Mean age, years (SD) [median, range]	11.5 (4.0) [11.5, 3.0-18.0]
Time since NF1 diagnosis, n (%)	
0 to 5 years	16 (19.5)
>5 to 10 years	28 (34.1)

level of pain interference with daily activities.

Caregiver proxy-reported response (N=82)		
Physical functioning	65.0 (24.3)	68.8 (3.1, 100.0)
Emotional functioning	54.9 (24.1)	50.0 (0.0, 100.0)
Social functioning	60.5 (26.1)	62.5 (0.0, 100.0)
School functioning	54.0 (24.4)	55.0 (0.0, 100.0)
Total	59.1 (20.6)	60.9 (15.2, 100.0)

***Abbreviations**: PedsQL: Pediatric Quality of Life Inventory; SD: standard deviation*

Table 2. EQ-5D-Y scores, child self-reported response (N=61)

Item	n (%)
Mobility	
No problems	47 (77.0)

directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Patients included have NF1 PN and are a paediatric population, so are relevant to the decision problem. Symptom severity varied so full population might not align with the decision

>10 to 15 years	26 (31.7)
>15 to 18 years	12 (14.6)
Time since PN diagnosis, n (%)	
0 to 5 years	26 (31.7)
>5 to 10 years	34 (41.5)
>10 to 15 years	18 (22.0)
>15 to 18 years	4 (4.9)
Number of PNs, n (%)	
1	33 (40.2)
2	26 (31.7)
3	8 (9.8)

Some problems	13 (21.3)	problem. Approximately one-third of patients were treated with surgery which may limit relevance to the decision problem.
A lot of problems	1 (1.6)	
Looking after myself		
No problems	46 (75.4)	
Some problems	13 (21.3)	
A lot of problems	2 (3.3)	
Doing usual activities		
No problems	32 (52.5)	
Some problems	26 (42.6)	
A lot of problems	3 (4.9)	
Having pain or discomfort		
No problems	21 (34.4)	
Some problems	29 (47.5)	
A lot of problems	11 (18.0)	
Feeling worried, sad, or unhappy		

4	4 (4.9)
5	2 (2.4)
>5	9 (11.0)
Symptoms of NF1-PN[a], n (%)	
Pain	53 (64.6)
Disfigurement	27 (32.9)
Motor dysfunction	23 (28.0)
Vision loss	13 (15.9)
Bowel or bladder dysfunction	11 (13.4)
Airway obstruction	4 (4.9)
Other	20 (24.4)

No problems	23 (37.7)
Some problems	31 (50.8)
A lot of problems	7 (11.5)
EQ-VAS	
Mean (SD)	77.6 (18.0)
Median (range)	82.0 (31.0, 100.0)

***Abbreviations**: VAS: visual analogue scale; SD: standard deviation*

Table 3. PROMIS scores: reported difficulties with movement in the last 7 days

Item	Mean (SD)	Median (range)
Child self-reported response (N=26)		
Mobility: T score	40.2 (8.6)	39.5 (33.0, 46.0)

None of the above	11 (13.4)
Comorbid conditions, n (%)	
ADHD	46 (56.1)
Headaches	39 (47.6)
Autism	15 (18.3)
Hypertension	11 (13.4)
Epilepsy	8 (9.8)
Vasculopathy	3 (3.7)
CHD	1 (1.2)
None of the above	14 (17.1)

***Abbreviations**: ADHD: attention-deficit hyperactivity disorder; CHD: congenital*

Upper Extremity Functioning: T score	39.5 (13.5)	39.5 (32.0, 49.0)
Caregiver proxy-reported response (N=20)		
Mobility: T score	36.0 (5.5)	35.0 (33.0, 40.5)
Upper Extremity Functioning: T score	29.1 (7.8)	29.0 (25.5, 34.0)

***Abbreviations**: SD: standard deviation*

Table 4. PII scores

Item	Mean (SD)	Median (range)
Child self-reported response		
All patients (N=61)	1.5 (1.8)	0.0 (0.0, 5.3)
Reported pain in the last 7 days (N=31)	3.0 (1.5)	3.3 (0.0, 5.3)

heart disease; NA: not applicable; SD: standard deviation

[a]Patients could be included in more than one category. Therefore, the sum of the percentages may exceed 100%.

Recruitment

Subjects participated in an online survey from December 1, 2020, to January 14, 2021. Participants were recruited via email through the NF Registry, a patient-centred database managed by the Children's Tumor Foundation

Caregiver proxy-reported response		
All patients (N=82)	1.3 (1.8)	0.0 (0.0, 6.0)
Reported pain in the last 7 days (N=39)	2.7 (1.8)	2.7 (0.0, 6.0)

***Abbreviations**: SD: standard deviation*

Table 4. Modified NRS-11 scores, child self-reported response

Item	Mean (SD)
All patients (N=61)	
Mean (SD)	2.7 (3.2)
Median (range)	1.0 (0.0, 10.0)
No pain (0), n (%)	30 (49.2)
Mild pain (1-3), n (%)	8 (13.1)
Moderate pain (4-6), n (%)	12 (19.7)

Severe pain (7-10), n (%)	11 (18.0)
Reported pain in the last 7 days (N=31)	
Mean (SD)	5.3 (2.4)
Median (range)	6.0 (1.0, 10.0)
Mild pain (1-3), n (%)	8 (25.8)
Moderate pain (4-6), n (%)	12 (38.7)
Severe pain (7-10), n (%)	11 (35.5)

***Abbreviations**: SD: standard deviation*

Yang 2022b [132]	Caregivers Caregivers of paediatric patients aged 2–18 years with NF1-PN were recruited to participate in an online survey administered between December 1, 2020 and January 14, 2021. Eligible caregivers had to be at least 18 years of age at the	US	95 caregivers of paediatric patients with NF1-PN met the eligibility criteria and participated	Burden reported for caregivers of paediatric patients with NF1-PN	Caregiver burden was assessed using the ZBI (designed to measure the caregiver's perceived level of burden as a result	ZBI caregiver burden score (N=95) • Mean (SD), 23.0 (13.8) • Median (range), 21.0 (0.0, 68.0) Level of burden based on ZBI caregiver burden score, n (%) • Little to no burden, 45 (47.4%) • Mild-to-moderate burden, 38 (40.0%) • Moderate-to-severe burden, 11 (11.6%)	**Consistency with DMC reference case:** HRQoL values are reported rather than utility values, which

time of survey participation, a primary caregiver of a paediatric patient with NF1-PN who was treatment naive or had been treated with selumetinib, a resident of the US, and able to read, write, and understand English
.

Population characteristics of caregivers (N=95)

Characteristic	Value
Female, n (%)	84 (88.4%)
Median age, years (range)	44.0 (18.0-70.0)
Race/ethnicity, n (%)	
White or Caucasian	81 (85.3)
Hispanic, Latino, or of Spanish origin	9 (9.5)
Asian or Pacific Islander	6 (6.3)

in the survey.

of caring for a patient)

- Severe burden, 1 (1.1%)

deviates from the DMCE preference.

The study took place in the US, which may not be directly relevant to clinical practice in Denmark.

Relevance to the decision problem: Data reported for caregivers of patients with NF1-PN, so are relevant to

Black or African American	3 (3.2)
American Indian or Alaska Native	**1 (1.1)**
Caregiver diagnosed with NF1, n (%)	
Yes	13 (13.7)
Caregiver diagnosed with PN, n (%)	
Yes	10 (10.5)
Employment status, n (%)	
Employed full time	39 (41.1)
Homemaker	22 (23.2)
Employed part time	18 (18.9)
Self employed	5 (5.3)
Long-term disability	4 (4.2)
Not employed, but looking for work	3 (3.2)

the decision problem.

[Approximately one-third of patients were treated with surgery which may limit relevance to the decision problem.]

Not employed and not looking for work	2 (2.1)
Short-term disability	1 (1.1)
Student	**1 (1.1)**
Retired	0 (0)
Health conditions, n (%)	
Anxiety	46 (48.4)
Depression	33 (34.7)
Obesity	24 (25.3)
Diabetes	5 (5.3)
Cancer	2 (2.1)
None of the above	35 (36.8)

***Abbreviations**: NF1: neurofibromatosis type 1; PN, plexiform neurofibroma*

	Characteristics of the paediatric patients are reported in Yang 2022 [131] Recruitment Caregivers were recruited from the NF Registry						
Yoshida 2022 [133]	Patients Adults with NF1 (N=73) (age- and sex-matched to 76 healthy volunteers without underlying diseases) Eligibility criteria included diagnosis of NF1 according to the NIH Consensus Conference criteria. Population characteristics **Characteristic / Value (NF1 patients) N=73 / Value (control N=76** Female, n (%) / 47 (64.4%) / 50 (66%	Japan	73 patients with NF1 were enrolled in the study; compared with 76 healthy volunteers (age and sex matched control) without underlying diseases	HRQoL reported for patient populatio n, all had NF1. Data for PN incidence not reported for all patients, but 63.3% of the 30/73 patients with Stage 5 disease had PNs.	HSUV were assessed using the EQ-5D-5L. A Japanese valuation algorithm was used to estimate utility scores [134]. The study was cross-sectional; therefore, patients were assessed at one timepoint only.	EQ-5D-5L index score, mean (SD) • NF1 patients, 0.738 (0.137) • Healthy volunteers, 0.951 (0.097), p<0.0001	**Consistency with DMC reference case:** Health utility values were elicited using the EQ-5D-5L, in line with the DMC preference. The study took place in Japan, and valued utilities using a Japanese value set,

Mean age, years (SD)	44.16 (14.87)	44.18 (15.63)
Severity (DNB classification), n		
Stage 1	5 (6.9)	NA
Stage 2	30 (41.1)	NA
Stage 3	6 (8.2)	NA
Stage 4	2 (2.7)	NA
Stage 5	30 (41.1)	NA

***Abbreviations**: NA, not applicable; SD: standard deviation*

Recruitment
Patients were referred to the Department of Dermatology of Tottori University Hospital and the Department of

HRQoL for specific adverse events are not reported

which may not be directly relevant to clinical practice in Denmark.

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

Dermatology of Fukuoka University Hospital, Japan		and symptomatic, which deviates from the decision problem.

A list of studies included in the HRQoL stream of the SLR can be found in table 68, alongside reasoning for exclusion.

Table 76. List of studies included in the HRQoL SLR

#	Study name	Citation
1	SPRINT: Phase II, Stratum 1	Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. New England Journal of Medicine 2020;382:1430-1442.
2		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.
3		Wolters P, Gross AM, Martin S et al. Prospective patient-reported outcome (PRO) measures document long-term 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 (AZD6244, ARRY-142886) Prospective patient-reported outcome (PRO) measures document long-term 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 (AZD6244, ARRY-142886). Presented at Children's Tumor Foundation NF Conference 2022
4	SPRINT: Phase II, Stratum 1	Gross AM. Selumetinib in Children with Neurofibromatosis Type 1 and Asymptomatic Inoperable Plexiform Neurofibroma At Risk for Developing Tumor-Related Morbidity. Neuro Oncol. 2022 Apr 25:noac109. doi: 10.1093/neuonc/noac109
5	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.
6		Hamoy-Jimenez, G., Elahmar, H.A., Mendoza, M. *et al.* A cross-sectional study of gender

		differences in quality of life domains in patients with neurofibromatosis type 1. Orphanet J Rare Dis. 2022;17, 40
7	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.
8	Lo 2021	Lo SH, Yoo HK, Lawrence C et al. Time Trade-Off Utilities for Neurofibromatosis type 1 (NF1) with Plexiform Neurofibromas (PN) Health States. Presented at 2021 NF Virtual Conference; June 14-16, 2021.
9	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.
10	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.
11	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.
12	Weiss 2021 (NCT02096471)	Weiss BD, Wolters PL, Plotkin SR, et al. NF106: A Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK Inhibitor Mirdametinib (PD-0325901) in Adolescents and Adults With NF1-Related Plexiform Neurofibromas. J Clin Oncol. 2021 Mar 1;39(7):797-806.
13	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.
14	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.
15	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.
16	Yang 2022	Yang X, Yoo HK, Amin S, et al. Clinical and humanistic burden among pediatric patients with neurofibromatosis type 1 and plexiform neurofibroma in the USA. Childs Nerv Syst. 2022 Aug;38(8):1513-1522
17	Yang 2022b	Yang X, Yoo HK, Amin S, et al. Burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN) in the United States: A Cross-Sectional Study. Neurol Ther. 2022 Sep;11(3):1221-1233
18	Yoshida 2022	Yoshida Y, Ehara Y, Koga M, et al. Health-related quality of life in patients with neurofibromatosis 1 in Japan: A questionnaire survey using EQ-5D-5L. J Dermatol. 2022 Jul 3. doi: 10.1111/1346-8138.16510

Table 77. List of studies excluded in the HRQoL SLR at full-text review and reasoning for exclusion

#	Citation	Reason for exclusion
1	Ahlawat S, Ly KI, Fayad LM, Fisher MJ, Lessing AJ, Berg DJ, Salamon JM, Mautner VF, Babovic-Vuksanovic D, Dombi E, Harris G, Plotkin SR, Blakeley J; REiNS International Collaboration. Imaging Evaluation of Plexiform Neurofibromas in Neurofibromatosis Type 1: A Survey-Based Assessment. Neurology. 2021 Aug 17;97(7 Suppl 1):S111-S119	Outcome: cost/resource use data

2	Al-Mulla, A. Neurofibromatosis Type 1 Patients with Plexiform Neurofibromas Treated with Selumetinib. Pediatric Blood and Cancer. 2020. 69(SUPPL 2):S37.	Outcome: Very limited data: only reports change in pain/function with no details of tools administered
3	Buono FD, Sprong ME, Paul E, et al. The mediating effects of quality of life, depression, and generalized anxiety on perceived barriers to employment success for people diagnosed with Neurofibromatosis Type 1. Orphanet J Rare Dis. 2021 May 21;16(1):234	Reported QoL (not HSUV) [SF-12, GAD-7, PHQ-9] in patients with NF1, but not with PN
4	Copley-Merriman C, Yang X, Juniper M, et al. Natural History and Disease Burden of Neurofibromatosis Type 1 with Plexiform Neurofibromas: A Systematic Literature Review. Adolesc Health Med Ther. 2021 May 19;12:55-66	SLR of natural history, disease burden, and treatment patterns among patients diagnosed with NF1 and PN
5	Crawford H, North K, Wilson MJ, et al. Development and preliminary evaluation of the Neurofibromatosis Type 1 Adult Quality of Life (NF1-AdQoL) questionnaire. Clin Exp Dermatol. 2022 Feb;47(2):271-281	Reported QoL (not HSUV) [NF1-AdQoL) in patients with NF1, but not with PN
6	Depping MK, Uhlenbusch N, Härter M, et al. Efficacy of a Brief, Peer-Delivered Self-management Intervention for Patients With Rare Chronic Diseases: A Randomized Clinical Trial. JAMA Psychiatry. 2021 Jun 1;78(6):607-615	Reported QoL (not HSUV) [SF-12) in patients with NF1, but not with PN
7	Doorley JD, Greenberg J, Bakhshaie J, et al. Depression explains the association between pain intensity and pain interference among adults with neurofibromatosis. J Neurooncol. 2021 Sep;154(2):257-263	Reported QoL (not HSUV) [PHQ-9, GAD-7, GCPS, PROMISv1) in patients with NF1, but not with PN
8	Doser K, Belmonte F, Andersen KK, et al. School performance of children with neurofibromatosis 1: a nationwide population-based study. European Journal of Human Genetics : EJHG. 2022 Jul. DOI: 10.1038/s41431-022-01149-z	Reported school performance in patients with NF1, but not with PN
9	Ejerskov C, Gaustadnes M, Ostergaard JR, et al. Exploring associations between constipation, severity of neurofibromatosis type 1 and NF1 mutational spectrum. Sci Rep. 2021 Apr 28;11(1):9179	Reported QoL (not HSUV) [3-item questionnaire on perceptions of NF1] in patients with NF1, but not with PN
10	Fertitta L, Bergqvist C, Armand ML, et al. Quality of life in	Reported QoL (not HSUV) [cNF-Skindex] in patients with NF1, but

	neurofibromatosis 1: development and validation of a tool dedicated to cutaneous neurofibromas in adults. J Eur Acad Dermatol Venereol. 2022 Aug;36(8):1359-1366	not with PN (subjects completed EQ-5D, but data NR)
11	Fishbein NS, Vranceanu AM, Mace RA. Baseline characteristics of adults with neurofibromatosis enrolled on a psychosocial randomized controlled trial. J Neurooncol. 2022 Sep;159(3):637-646	Reported QoL (not HSUV) [WHOQOL-BREF] in patients with NF1, but not with PN
12	Foji S, Mohammadi E, Sanagoo A, et al. The Patients' Experiences of Burden of Neurofibromatosis: A Qualitative Study. Iran J Nurs Midwifery Res. 2021 Jul 20;26(4):342-348	Reported QoL (not HSUV) [face-to-face interview on burden of NF] in patients with NF1, but not with PN
13	Geoffray MM, Robinson L, Ramamurthy K, et al. Predictors of cognitive, behavioural and academic difficulties in NF1. J Psychiatr Res. 2021 Aug;140:545-550	Reported QoL (not HSUV) [cognitive, behavioural ability] in patients with NF1, but not with PN
14	Gregory TA, Molina PSB, Phillips GD et al. Impact of neurofibromatosis type 1 in an adult community population. Neuro-Oncology Practice. 2022; 9 (3); 229–235	Reported QoL (not HSUV) [survey assessing psychosocial wellbeing and impact of COVID-19] in patients with NF1, but not with PN
15	Gross AM. Using real world data to support regulatory approval of drugs in rare diseases: A review of opportunities, limitations & a case example. Curr Probl Cancer. 2021 Aug;45(4):100769	Study design: Review of utility and limitations of external controls for regulatory approval of drugs in rare diseases (case study with NF1)
16	Johansson E, Kallionpää RA, Böckerman P, et al. The rare disease neurofibromatosis 1 as a source of hereditary economic inequality: Evidence from Finland. Genet Med. 2022 Apr;24(4):870-879	Reported impact on employment in patients with NF1, but not with PN
17	Leppich K, Schneider J, Eismann C et al. Psychosocial and Socioeconomic Factors in Children with Neurofibromatosis Type 1. Journal of Pediatric Neurology 2022; 20(3): 188-193	Reported QoL (not HSUV) [psychosocial outcomes] in patients with NF1, but not with PN
18	Mace RA, Doorley J, Bakhshaie J, et al. Psychological resiliency explains the relationship between emotional distress and quality of life in neurofibromatosis. J Neurooncol. 2021 Nov;155(2):125-132	Reported QoL (not HSUV) [WHOQOL-BREF] in patients with NF1, but not with PN
19	Maguiness S, Berman Y, Rubin N, et al.; REiNS International Collaboration. Measuring the	Reported QoL (not HSUV) [Skindex-29] in patients with NF1,

	Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1. Neurology. 2021 Aug 17;97(7 Suppl 1):S25-S31	but with cutaneous neurofibroma, not PN
20	Roy A, Roulin JL, Gras-Le Guen C, et al. Executive functions and quality of life in children with neurofibromatosis type 1. Orphanet J Rare Dis. 2021 Oct 9;16(1):420.	Reported QoL (not HSUV) [Kidscreen-52 questionnaire] in patients with NF1, but not with PN
21	Shahrestani S, Brown NJ, Strickland BA, et al. The role of frailty in the clinical management of neurofibromatosis type 1: a mixed-effects modeling study using the Nationwide Readmissions Database. Neurosurg Focus. 2022 May;52(5):E3	Reported QoL (not HSUV) [JHACG frailty-defining diagnosis indicator] in patients with NF1, but not with PN
22	Vasiljevski ER, Burns J, Bray P, et al. L-carnitine supplementation for muscle weakness and fatigue in children with neurofibromatosis type 1: A Phase 2a clinical trial. Am J Med Genet A. 2021 Oct;185(10):2976-2985	Reported QoL (not HSUV) [Pediatric Quality of Life and Child Behavior Checklist for ages 6–18] in patients with NF1, but not with PN
23	Wolters PL, Reda S, Martin S, et al. Impact of the coronavirus pandemic on mental health and health care in adults with neurofibromatosis: Patient perspectives from an online survey. Am J Med Genet A. 2022 Jan;188(1):71-82.	Reported QoL (not HSUV) [behavioual conditions] and resource use in patients with NF1, but not with PN
24	Wolters PL, Vranceanu AM, Thompson HL, ey al; REiNS International Collaboration. Current Recommendations for Patient-Reported Outcome Measures Assessing Domains of Quality of Life in Neurofibromatosis Clinical Trials. Neurology. 2021 Aug 17;97(7 Suppl 1):S50-S63	Review and recommendation of PROs to use as clinical endpoints in medical and psychosocial trials for children and adults with NF11/2 and schwannomatosis
25	Yang X, Desai K, Agrawal N, et al. Characteristics, treatment patterns, healthcare resource use, and costs among pediatric patients diagnosed with neurofibromatosis type 1 and plexiform neurofibromas: a retrospective database analysis of a medicaid population. Curr Med Res Opin. 2021 Sep;37(9):1555-1561	Outcome: reports HRQoL data
26	Yang X, Yoo HK, Amin S, et al. RARE-06. CLINICAL BURDEN AMONG PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 (NF1) AND PLEXIFORM	Superseded by 2022 full publication

	NEUROFIBROMA (PN) IN THE UNITED STATES (US). Neuro Oncol. 2021 Jun 1;23(Suppl 1):i41–2.	
27	Yang X, Yoo HK, Amin S, et al. Health-related quality of life (HRQoL) among pediatric patients with neurofibromatosis type 1 (NF1) and plexiform neurofibroma (PN) in the United States (U.S.). Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 10042-10042.	Superseded by 2022 full publication
28	Yang X, Yoo HK, Amin S, et al. QOLP-02. HEALTH-RELATED QUALITY OF LIFE (HRQOL) AMONG PEDIATRIC PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 (NF1) AND PLEXIFORM NEUROFIBROMA (PN) IN THE UNITED STATES: PERSPECTIVES OF THE PATIENTS AND CAREGIVERS, Neuro-Oncology 2021; 23 (Supplement_6);vi182–vi183	Superseded by 2022 full publication

Appendix I – Mapping of HRQoL data

See appendix H.

Appendix J – Probabilistic sensitivity analyses

In order to evaluate uncertainty associated with parameter precision, probabilistic sensitivity analyses (PSA) were conducted to establish the impact of such uncertainty. PSA included all model parameters; estimates of uncertainty were based on the uncertainty in the source data where data availability permitted this. The result of the analysis are described in Section 8.7.2.

All parameters were varied simultaneously, and multiple sets of parameter values were sampled from predefined probability distributions to characterize the uncertainty associated with the precision of mean parameter values.

Parameters can be sampled from appropriate statistical distributions, such as the following:

- Survival function parameters can be sampled from correlated distributions defined by their mean, standard error, and covariance.
- Mean costs can be sampled from a gamma distribution defined by the mean and standard error.

The parameters and their distribution included in the model PSA are reported in

Table 78. PSA values.

Table 78. PSA values

Variable	Value	Measurement of Uncertainty (Distribution)
Patient characteristics		
BSA Linear regression constant	0.387	Beta (probability/proportion [0,1])
BSA Linear regression age	0.085	Beta (probability/proportion [0,1])
Utility Age Regression Constant Value	0.950	Beta (probability/proportion [0,1])
Utility Age Regression Male Value	0.021	Beta (probability/proportion [0,1])
Utility Age Regression Age value	$-2.5*10^{-5}$	Beta (probability/proportion [0,1])
Utility Age Regression Age^2 Value	$-3.3*10^{-6}$	Beta (probability/proportion [0,1])
Survival analysis (within-trial comparison)		
PFS – Cumulative probability of progression	16%	Beta (probability/proportion [0,1])
PFS – Distribution	Weibull	Cholesky
PFS – Distribution	Generalised Gamma	Cholesky
PFS – Distribution	Exponential	Cholesky
PFS – Distribution	Loglogistic	Cholesky
PFS – Distribution	Lognormal	Cholesky
PFS – Distribution	Gompertz	Cholesky
PFS – Distribution	Gamma	Cholesky
Treatment discontinuation for Koselugo®		
TTD	Weibull	Cholesky

TTD	Generalised Gamma	Cholesky
TTD	Exponential	Cholesky
TTD	Loglogistic	Cholesky
TTD	Lognormal	Cholesky
TTD	Gompertz	Cholesky
TTD	Gamma	Cholesky
Treatment duration cap (years)	8.0	Gamma (Positively skewed >0)
Dose interruption weighting		
Koselugo®	92.27%	Beta (probability/proportion [0,1])
HSUV and related values		
Progression-free (Koselugo®)	0.510	Beta (probability/proportion [0,1])
Progressed disease (BSC)	0.740	Beta (probability/proportion [0,1])
Years to achieve treated HRQoL	1	Gamma (Positively skewed >0)
Years to revert to untreated HRQoL	5	Gamma (Positively skewed >0)
Number of caregivers	1.72	Gamma (Positively skewed >0)
Parents age at birth (proportional change)	32.5	Gamma (Positively skewed >0)
Mean age of parents	45	Gamma (Positively skewed >0)
Caregiver's mean utility	0.720	Beta (probability/proportion [0,1])
Parents age at birth (absolute shortfall)	32.5	Gamma (Positively skewed >0)
Absolute reduction in HRQoL for caregiver	0.046	Beta (probability/proportion [0,1])

Appendix K – HSUV related study

12.1 Vignette-based time-trade-off study

To account for the evidence gaps mentioned in Section 8.4 and to facilitate the cost-effectiveness analysis, a vignette-based time-trade-off (TTO) study was conducted. 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 when 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 10 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 [135, 136].

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 [135]. 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).

12.1.1 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).

12.1.1.1 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.

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, to ensure that the experience of patients was accurately represented within the vignettes. Draft vignettes were revised iteratively after interviews with the clinical experts, and subsequently, after adult patient and parent/carer interviews (described in Part II).

12.1.1.2 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. Potential participants were asked to complete a brief screening questionnaire to confirm that they met the inclusion criteria and flexible quotas set to achieve purposive sampling. The aim was 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).
• The NF1 PN patient had never been treated with selumetinib, nor with binimetinib, cobimetinib, mirdametinib or trametinib (off-label treatments sometimes used in this population).
• The 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. Interviews were conducted individually over the telephone or via an online video call lasting approximately 1 hour each.

12.1.1.3 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. Participants were eligible if they were adults (aged ≥18 years).
A total of 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 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 that there was 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

NF1 PN is a heterogeneous disease and the impact of symptoms varies according to PN location. However, the relative differences between untreated and treated values did not differ significantly between the alternatively specified PN locations (Table 71). This validates and supports the use of the unspecified PN location vignettes. The finalised vignettes, participant details and relevant results for the cost-effectiveness analysis are presented below and are considered representative of the average utility in the NF1 patient population:

• Untreated paediatric patient with unspecified PN location (referred to as paediatric patient without selumetinib).
• Treated paediatric patient with unspecified PN location (referred to as paediatric patient with selumetinib).

Table 71. 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 study are presented in Table 72. The population recruited to value the vignette health states was a representative sample of the UK general public.

Table 72. Sample characteristics from valuation interviews (n=100)

Characteristics		UK sample for TTO valuation (n=100)
		Mean (SD)
Age, years		42.0 (16.4)
		n (%)
Sex	Male	49 (49%)
	Female	51 (51%)
Ethnicity	White	80 (80%)
	Asian	6 (6%)
	Black	5 (5%)
	Mixed	8 (8%)
	Other	1 (1%)

TTO: time-trade-off

VAS ratings

The mean VAS ratings for the health state vignettes are presented in Table 68. Table 69 shows the TTO ratings for the health state vignettes.

Table 73. VAS ratings for health state vignettes (n=100)

Health state	Mean (SD)	SE	95% CI
Paediatric patient without selumetinib	43.7 (20.5)	2.1	39.6, 47.8
Paediatric patient with selumetinib	63.2 (17.8)	1.8	59.7, 66.7

Table 74. TTO ratings for health state vignettes (n=100)

Health state	Mean (SD)	SE	95% CI
Health state	Mean (SD)	SE	95% CI
Paediatric patient without selumetinib	0.51 (0.37)	0.037	0.438, 0.583

The use of utilities from health states representing an unspecified PN location for the 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 0.223 to 0.242 (

Table 75). This supports the use of utilities for the health states with an unspecified PN location, with the objective of being more representative of the NF1 PN patient population as a whole.

Table 75. Utility value differences with and without selumetinib

PN location	Difference in utility value with and without selumetinib
Unspecified (base case)	0.230
Face	0.223
Trunk	0.242
Leg	0.233