NICE National Institute for Health and Care Excellence

Part 1	No confidential information
Public handouts	

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

1st Evaluation committee meeting

Lead team presentation

Chair: Peter Jackson

Lead team: Mark Sheehan, Matt Smith, Sarah Davis

Evidence Review Group: Kleijnen Systematic Reviews

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Company: AstraZeneca

10th November 2021

Key issues

Issue	Slide(s)	Impact
1 Long-term clinical effectiveness of selumetinib and BSC	15	
2 • Lack of direct comparison between selumetinib and BSC • Generalisability of SPRINT to UK practice	16-17	
3 Model structure	24-26	
4 Modelling of progression	28-29	
5 Quality of life data and utility values used within the model	30-33	
6 Carer's disutility values used within model and number of carers	34-35	
7 Utility waning after progression	36-37	
8 Costs not included in the model	38-39	

Disease background

Disease background

Cause

- Defect in the NF1 gene, situated at chromosome 17q11.2
- PNs are a neurological manifestation from nerve fascicles that grow along length of nerve

Diagnosis

- NF1 genetic testing and meeting clinical criteria
- Most NF1 PNs diagnosed in early childhood and grow most rapidly during this period.

Disease course

- Children experience uncontrolled and unpredictable growth of PN
- PN were found to grow most rapidly in children <18 years old, with the highest PN growth rates being observed in young children and growth rates plateau by 12–18 years of age
- PNs rarely decrease in volume spontaneously, PN growth associated with morbidity and mortality
- Some people with NF1 are more at risk of malignant peripheral nerve sheath tumours

Aims of treatment

- Complete surgical resection is often not feasible → regrowth been observed
- Treatment may include physiotherapy, psychological support and pain management
- Effective medical therapies are lacking, other treatments aimed at reducing symptoms

Disease background - symptoms

PN can affect multiple body regions and can reach extremely large sizes. The majority of PN are symptomatic, and are associated with severe morbidities

Morbidity	Description
Pain	Common source of neuropathic pain and neurologic dysfunction. Associated with use of scheduled, neuropathic and opioid pain medication
Motor	Restrict range of motion or cause pain may lead to impaired motor function. PN growth can put pressure on spinal nerves → muscle weakness/disability
Airway	PN near airways can lead to airway obstruction, which requires patients to undergo tracheostomies, and in some cases leads to death. Airway PN can also cause morbidities such as sleep apnoea
Bladder and Bowel	PN growth can impede the function of these organs e.g., incontinence. Growth of PN can result in severe complications → bowel obstruction or blood in the urine
Vision	Growth of PN around the eye and eyelid can cause significant visual loss and prevent the eye from achieving normal visual acuity, cause eye pain, drooping of the eyelid (ptosis) and severe protrusion of the eye (proptosis). Patients with orbital and periorbital PN are at risk of developing glaucoma and optic nerve disease due to compression, especially if the PN grows rapidly
Disfigurement	The growth and development of visible PN, such as those on the head and neck, can result in severe disfigurement

Source: Company submission

Selumetinib, Koselugo®

Marketing authorisation granted June 2021	Treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged three years and above
Mechanism of action	Potent, selective, small molecule inhibitor of MEK1/2
Administration	Oral capsules of 10 mg and 25 mg
Dosage	Selumetinib is administered at a dose of 25 mg/m^2 BSA twice daily, up to a maximum single dose of 50 mg.
Duration	Treatment with selumetinib should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. 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.
Eligible UK population	Company estimate 37 patients eligible for treatment per year ERG estimate 70 patients eligible for treatment per year
List price	Per pack of 60 capsules: 10mg £4,223.59, 25mg £10,560.00 Cost per year depends on dosing schedule. Ranges from £77,133 (BSA 0.55–0.69 m2) – £257,135 (BSA 1.90–1.94 m2) A confidential patient access scheme has been approved.

Source: Company submission

BSA: body surface area; MEK: mitogen-activated protein kinase; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Treatment pathway: company suggested positioning

Treatment centres

Treatment delivered by the two specialist UK centres:

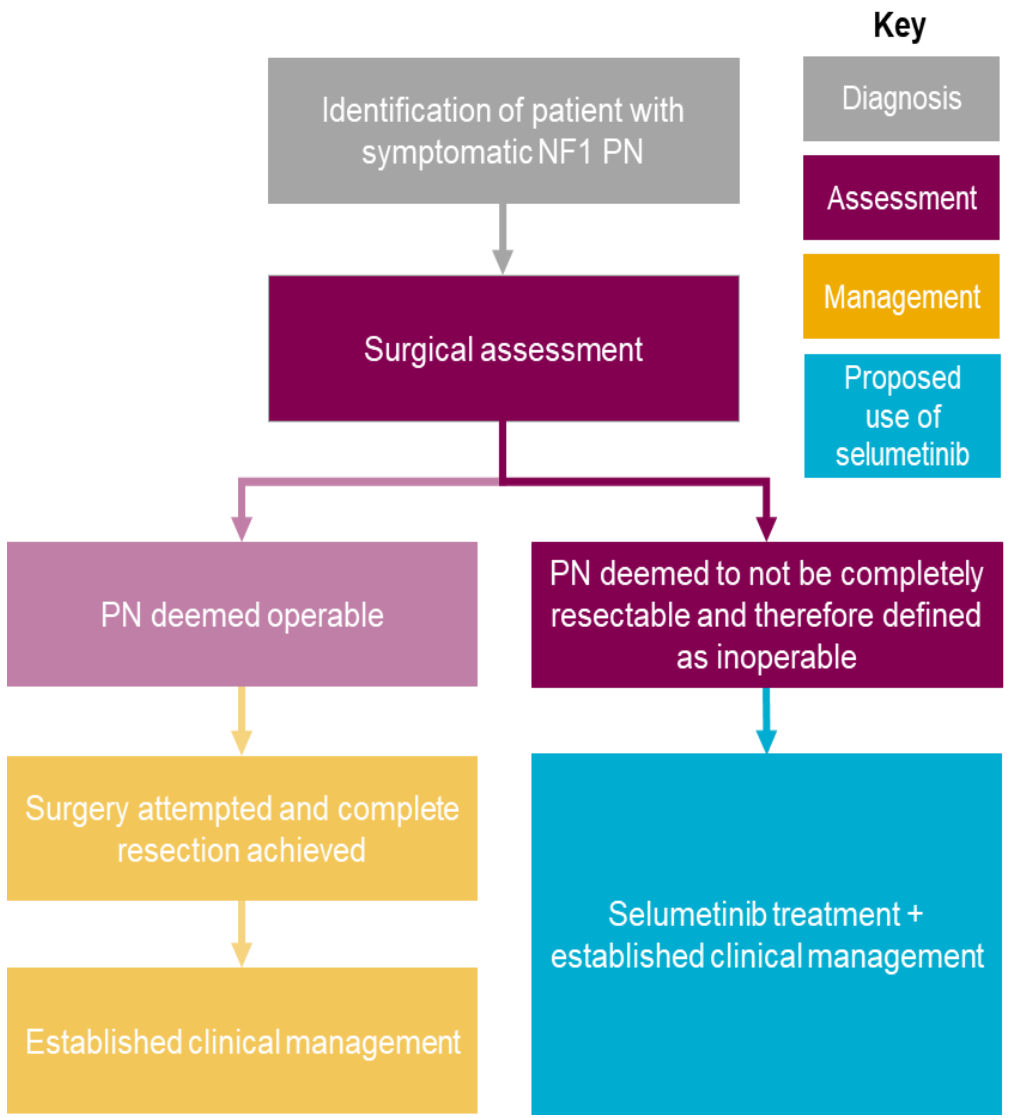
- Guy's and St Thomas' NHS Foundation Trust (Evelina London Children's Hospital)
- Manchester University NHS Foundation Trust (St Mary's, Manchester).

Current treatments

- surgery and symptom management
- PN for which only partial resection can be achieved are considered 'inoperable'

Selumetinib

- will provide access to first disease-modifying treatment for NF1 PN
- provide a pharmacological option for patients with symptomatic PN that are inoperable



Source: Company clarification response, figure 1.

NF1: neurofibromatosis type 1; PN: plexiform neurofibroma

NHS England and Improvement perspective

- Pathway well defined. Selumetinib if approved:
  - would not alter the current pathway of care
- No national NHS England clinical commissioning policies for NF1
- Selumetinib would be administered through existing commissioning arrangements
  - 2 specialist centres in the NHS
  - currently deliver services for people with complex neurofibromatosis
- Rules for stopping and starting treatment will be developed as necessary

Professional submissions [1]

British Paediatric Neurology Association and Clinical experts

Current treatment – 3 main treatment pathways for children with symptomatic PN

Children with NF1 PN are seen within the national commissioned services in Manchester or London. 3 main treatment options:

- conservative (which includes pain management)
- surgery
- medical treatments; MEK inhibitors (trametinib in clinical trials and compassionate use, not licensed in NF1 PN)

Place in current practice

- Highly specialised service (Manchester and London), see on average 150 children per year. Of these, anticipate that 5-10 per year will be eligible to receive selumetinib
- Eligibility criteria for consideration of in line with the initial NCI trials.
- All NF1 children with symptomatic PN should be seen within the national service and decisions with regards to MEKi be made in the national MST meeting as is current practice
- Children will benefit from the expertise of the multidisciplinary team.
- Otherwise may be denied other more suitable treatment options e.g., surgery or be subjected to a potentially harmful treatment that they are unlikely to benefit from
- If MDT agrees that MEKi is best treatment option, anticipate selumetinib will be delivered and monitored in designated local oncology units pending their agreement

MDT: multi-disciplinary team; MEKi: mitogen-activated protein kinase inhibitor; NCI: National Cancer Institute; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Professional submissions [2]

British Paediatric Neurology Association and Clinical experts

Clinical evidence

Some evidence of PN partial volume reduction, but data is lacking:

- Small numbers of people evaluated
- Clinical heterogeneity (PN in different locations cause different symptoms)
- Clinical outcome measures are more important than radiological volume reduction
- Not comparable control group in clinical trials
- Single arm, open label Phase I/II study of selumetinib is ongoing in London (INSPECT trial)

Selumetinib

- No current alternative for inoperable PN in children
- Only available as a capsule preparation and therefore not suitable for very young children
- More frequent hospital visits to monitor side effects

Trial population relevance to clinical practice

Trial population will differ slightly from those discussed in MEKi MDT for 2 main reasons:

- People are deemed ‘inoperable’ on referral but discussed at MDT and decision may differ
- Trial population generally more symptomatic from their PN than seen in complex NF1 clinics. However people then put forward for MEKi would reflect the types of patients taking part in the NCI trial

MDT: multidisciplinary team; MEKi: mitogen-activated protein kinase inhibitor; NCI: National Cancer Institute; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Patient and carer group submissions

Patient and carer experiences

Company submission – qualitative interviews

Patients

- Children with NF1 PN are often unable to participate in educational and social activities due to the impact of PN-associated morbidities, which has a substantial emotional impact on both the child and their family
- Disfigurement may make children with NF1 PN more vulnerable to bullying, further exacerbating the emotional and psychological burden of the disease
- Adult patients stated that they had experienced bullying, stigma or social exclusion due to their disease at some point in their lives
  - "this tumour is shredding my nerves day by day, both literally and figuratively"

Patient and carer experiences

Company submission – qualitative interviews

Carers

- Parents and carers of paediatric patients with NF1 PN describe providing multiple types of support, such as arranging and managing care through hospital appointments, managing patient symptoms, supporting daily activities, and providing educational, emotional and physical support to their child
- [redacted]
  - [redacted]

Patient and carer group submissions [1]

Submission from Childhood Tumour Trust

Unmet need

- Parents feel that often there is no option for their child
- Currently treatment options are very limited
  - radiotherapy should not be used
  - surgical removal is complex and often cannot be fully removed
  - pain relief can be difficult to get right and nerve pain is very difficult to manage

Quality of life

- Affects all aspects of life
- Co-morbidities such as learning disabilities, autism, ADHD or mental health problems, severe physical impact affecting mobility, disfigurement and significant pain
- Unpredictable → managing and living with the condition harder
- Pain management can be poor → impact all aspects of daily living
- Social and societal impact of having a plexiform neurofibromas. Especially with disfigurement and the emotional and mental health implications of the diagnosis
- Selumetinib treatment may have less of a negative impact upon quality of life compared to conventional treatment e.g. surgery

ADHD: attention deficit hyperactivity disorder

Patient and carer group submissions [2]

Submission from Childhood Tumour Trust

Selumetinib

Advantages	Disadvantages
Non invasive/Non surgical treatment	New treatment may not be available to everyone
Can be used to treat inoperable plexiform neurofibromas	Knowledge of treatment is not widespread
Less impact upon quality of life compared to conventional treatment	Cost implications
No repeated surgical treatment	Long-term outcomes of selumetinib unknown
Less impact on development and education	
Reduced pain and reduced need for long term pain medication	
Reduced impact on the patients mental health	
Easier for the patients family to manage	

Decision problem

	Final scope NICE	Variation from scope in company submission	ERG comments
Population	Children aged three years and over with symptomatic and inoperable PN associated with NF1	None	In line with NICE scope. trials included for efficacy and safety data are single arm trials.
Intervention	Selumetinib	None	In line with NICE scope
Comparators	Established clinical management without selumetinib	Established clinical management without selumetinib, including pain management	In line with NICE scope
Outcomes	Complete and partial response rate; Growth rate of PN; Disfigurement; Physical functioning; Visual function; Airway functioning; Bowel and bladder continence; Pain; Adverse effects of treatment HRQoL (children)	In addition to those detailed in the final scope, the following relevant outcomes will be presented: Duration of response; PFS; Time to progression; Global impression of change	In line with NICE scope

HRQoL: health related quality of life; NF1: neurofibromatosis type 1; PFS: progression free survival; PN: plexiform neurofibromas

Clinical trial: ongoing

	SPRINT Phase II Stratum I, n=50 (trial start date: August 2015)
Trial design	Interventional, single arm, open label
Population	Patients aged 2–18 with NF1 and symptomatic, inoperable PN
Location	US (four study centres)
Control arm	N/A (single arm trial)
Key inclusion criteria	Aged 2-18 and with a diagnosis of NF1 with inoperable and symptomatic PN
Follow up	Long-term safety follow-up was planned for 7 years from initiation of treatment, or 5 years after completion of treatment, whichever takes longer
Dose	25 mg/m^2 BSA twice a day
1º endpoints	ORR to selumetinib, defined as the rate of confirmed PR and CR (PR defined as PN decrease ≥20% compared to baseline; CR defined as the disappearance of the target PN) using centrally read volumetric MRI
2º endpoints	Tumour volumetric responses: Best objective response, duration of response, effect on PN growth rate, time to progression and progression free survival Clinical outcome measures: Pain, motor function, airway function, visual function, disfigurement, physical functioning
HRQoL	PedsQL questionnaire

◉ *Does SPRINT provide long-term clinical effectiveness for selumetinib?*

BSA: body surface area; CR: complete response; HRQoL: health related quality of life; MRI: magnetic resonance imaging; NF1: neurofibromatosis type 1; ORR: objective response rate; PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma; PR: partial response

Additional clinical evidence

ERG comments

- Data from two other studies could have been included in the company submission:

Study	ERG assessment of relevance to decision problem
Baldo et al. 2020	The company basis for non-relevance (small sample size and imprecision) is not an exclusion criterion for the SLR. The population and intervention are relevant and this study could have provided data on AEs
Espirito Santo et al. 2020	The company's basis for non-relevance (small sample size and categorical data) is not an exclusion criterion for the SLR. Some data are not categorical (e.g., duration of treatment). The population and intervention are relevant and this study could have provided data on AEs and duration of response

- ERG noted SPRINT was conducted in the US. However, the company submission states based on an assessment of baseline characteristics, patients from the SPRINT Phase II clinical trial are broadly representative of the UK paediatric NF1 PN patient population, which has been confirmed by clinical experts in the UK

AEs: adverse events; NF1: neurofibromatosis type 1; PN: plexiform neurofibroma; SLR: systematic literature review

Clinical evidence from SPRINT and external comparator studies

- In order to determine comparative effectiveness of selumetinib vs established clinical management, non-randomised comparisons vs external control data were explored
- Prior SLR identified 2 suitable studies reporting on the natural history, disease burden, and treatment patterns in NF1 PN:
  - naïve comparison between SPRINT Phase II Stratum I and an age-matched cohort of the NCI Natural History study
  - naïve comparison of progression free survival (PFS) between SPRINT Phase II Stratum I and patients with progressive PN from placebo arm of tipifarnib Study 01-C-02220222
- NCI Natural History study most aligned to SPRINT Phase II Stratum I in terms of using volumetric MRI to assess PN volume and median age. Provided most extensive data
- NCI Natural History study and tipifarnib Study 01-C-0222 were both carried out by the same group, NCI Paediatric Oncology Branch → same group which carried out SPRINT Phase II Stratum I and so the methodologies used are highly similar and comparable
- NCI Natural History study and tipifarnib Study 01-C-0222 were therefore considered the most appropriate external control for SPRINT Phase II Stratum I

◉ *At what age would treatment be started in clinical practice? Would use of selumetinib continue after the age of 18?*
◉ *Is the use of external controls as comparators appropriate?*
◉ *Is the population in SPRINT generalisable to the UK population?*

NICE

NCI: National Cancer Institute; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas; SLR: systematic literature review

Clinical effectiveness results

Baseline characteristics in trials

	SPRINT Phase II Stratum I n=50	Natural History Study age-matched cohort, n=93	Placebo arm of tipifarnib study 01-C-0222, n=29
Age, mean (SD)	[redacted]	7.8 (3.0 – 17.0)	8.2 (3 – 17.7)
Female, n (%)	[redacted]	36 (39)	15 (52)
Target PN volume at baseline, mL median (range)	[redacted]	354 (3.7 – 4895.0)	316 (39.6 – 4896)
Target PN status, n (%)			
Progressive	[redacted]	NR	29 (100)
Unprogressive	[redacted]	NR	0 (0)
Unknown	[redacted]	NR	0 (0)
Target PN location, n (%)			
Neck and trunk	[redacted]	13 (14)	NR
Neck and chest	[redacted]	NR	9 (31)
Trunk and limbs	[redacted]	17 (18)	3 (10)
Head only	[redacted]	13 (14)	NR
Face	[redacted]	NR	3 (10)
Head and neck	[redacted]	5 (5)	4 (14)
Trunk only	[redacted]	36 (39)	NR
Limbs only	[redacted]	8 (9)	1 (3)
Whole body	[redacted]	1 (1)	NR

Source: Company submission, tables C9 and C10

NICE

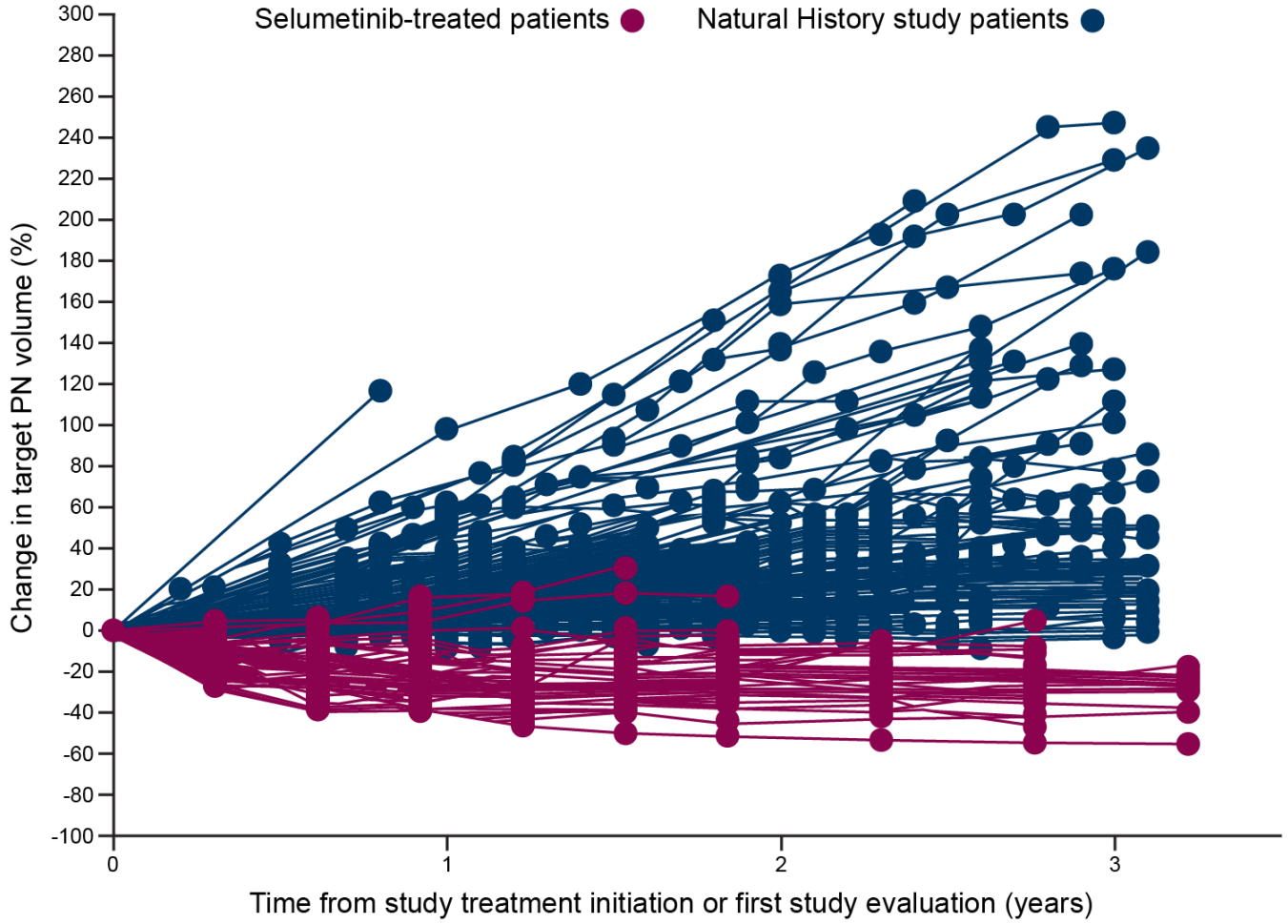
PN: plexiform neurofibromas; SD: standard deviation; NR: not reported

SPRINT Phase II Stratum I clinical effectiveness

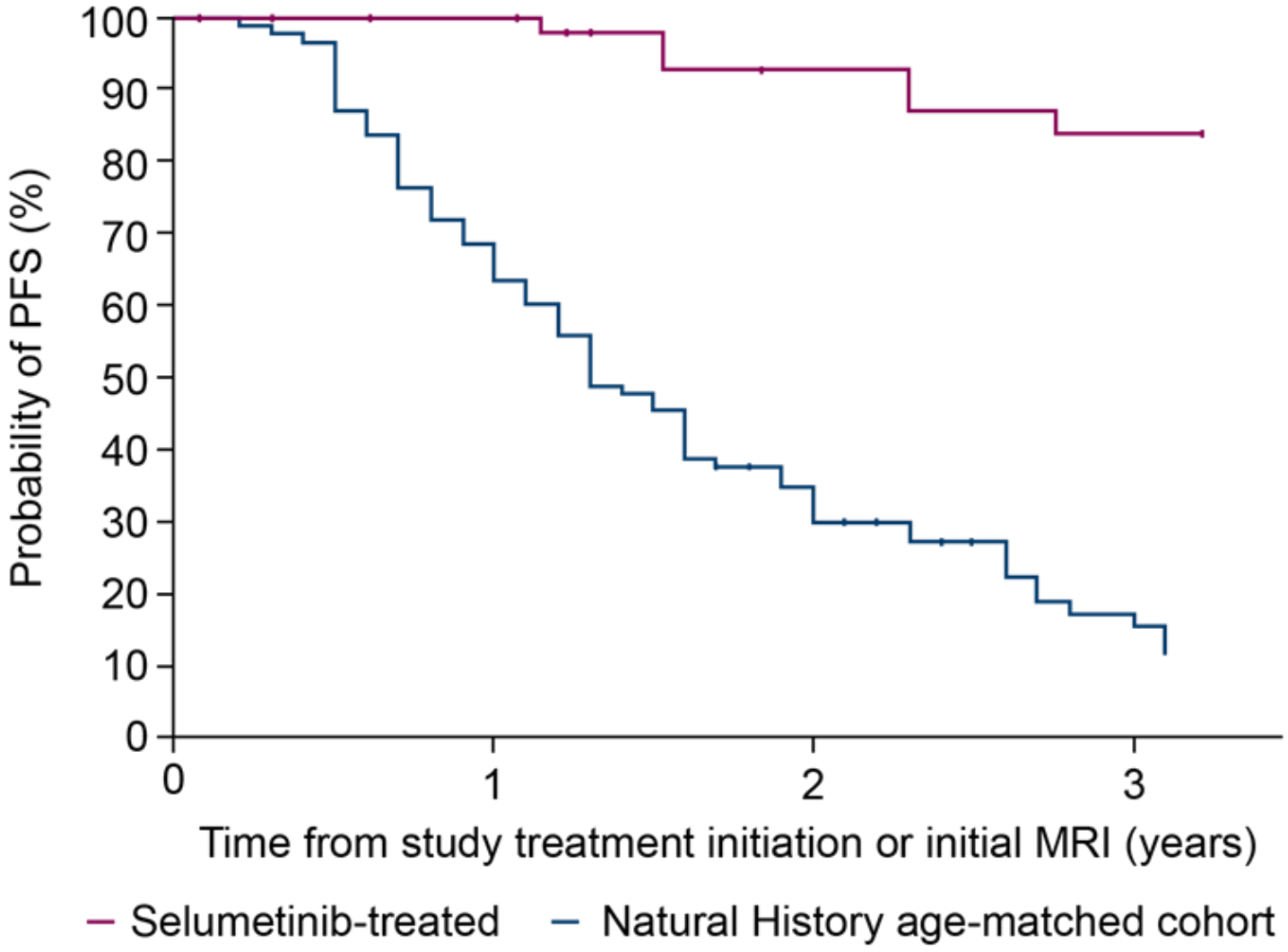
	SPRINT Phase II Stratum I n=50	Natural History Study age-matched cohort, n=93	Placebo arm of tipifarnib study 01-C-0222, n=29
Primary outcome			
ORR (%)	68	0	N/A
Secondary outcomes			
BOR of reduction in PN volume from baseline (%)	90	N/A	N/A
≥20% reduction in PN volume at BOR (%)	74	N/A	N/A
Median time to initial response	8 cycles	N/A	N/A
PN growth rate			
PN growth rate >20% per year, % (n)	**0 (0)**	**43 (40)**	N/A
Median change in PN volume, between baseline and most recent MRI, % (range)	**-23 (-55.1 – +30)**	**+77 (-40 – +1429)**	N/A
PFS			
Median PFS, years	**Not reached**	**1.3 (1.1 – 1.6)**	N/A
Probability of PFS at 3 years, %	**84**	**15**	N/A
Probability of PFS at 2 years, %	[redacted]	N/A	21

BOR: best objective response; ORR: objective response rate; MRI: magnetic resonance imaging; PFS: progression free survival; PN: plexiform neurofibromas; SD: standard deviation; N/A; not applicable

Change in target PN volume in SPRINT Phase II Stratum I compared to age-matched Natural History study control cohort



PFS in SPRINT Phase II Stratum I compared to age-matched Natural History study control cohort



Clinical evidence – SPRINT Phase II Stratum I Quality of life

- SPRINT Phase II Stratum I collected PedsQL self-reported and parent reported outcomes
- Also included assessments of PN-associated morbidities
  - pain
  - motor function
  - airway function
  - bowel/bladder function
  - visual function
  - disfigurement

ERG comments

- Company state that selumetinib has a positive, clinically meaningful impact on PN-associated pain. This is accurate for a large number of patients after 12 months treatment
- However, some people still experienced deterioration or no change in pain intensity or interference with daily functioning

SPRINT – summary of adverse events

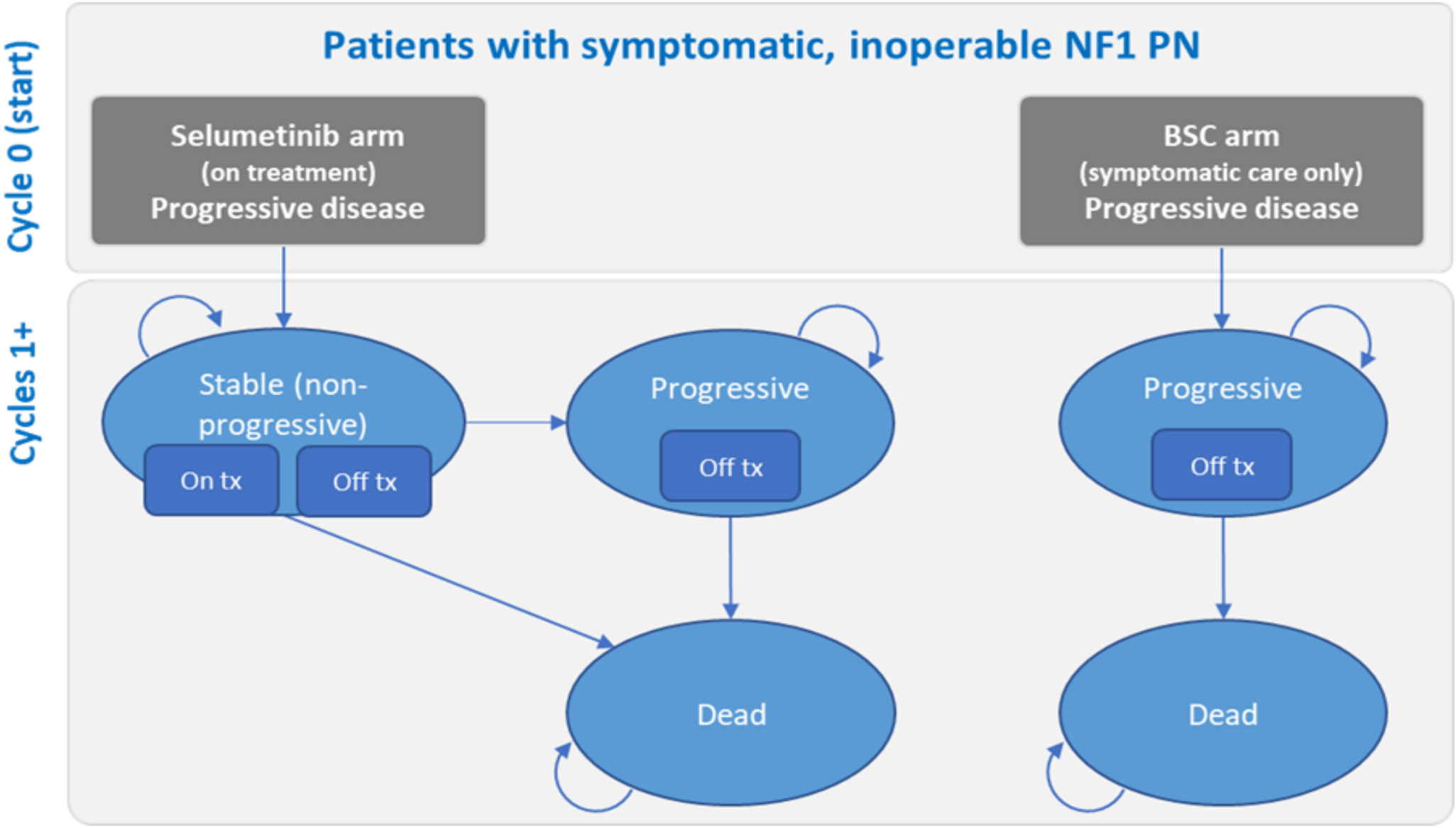
AEs	Selumetinib (N=50)
All grade AEs, n (%)	[redacted]
Grade ≥3 AEs, n (%)	[redacted]
Treatment-emergent grade ≥3 AEs, n (%)	[redacted]
SAEs, n (%)	[redacted]
Treatment-emergent SAEs[a], n (%)	[redacted]
Deaths, n (%)	[redacted]
Dose interruptions due to AEs, n (%)	[redacted]
Dose reductions due to AEs,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

- [redacted] of patients experienced AEs and [redacted] of patients experienced Grade ≥3 AEs. [redacted]
- The most common AEs of any grade were [redacted]
- The most common Grade ≥3 AEs were [redacted] All SAEs with known outcomes [redacted]

NICE AE: adverse events; DCO: data cut-off; SAE: serious adverse events

Health economics

Key issue 3: Model structure [1]



NICE BSC: best supportive care; tx: treatment

Key issue 3: Model structure [2]

Background

- Company used AUC approach with non-progressed, progressed or deceased states
  - BSC arm enter model at PD. Selumetinib arm enter model at PD but assumed to stabilise within first year of treatment and remain PF until progression
- Maximum duration of treatment was assumed until patients reach the age of 18
- Utility values depend on progression status and are adjusted for age-related disutilities
- Company assigned constant utility to PD in BSC → may underestimate selumetinib benefit
- Selumetinib arm accrue costs while on selumetinib, AE costs and MRI costs. BSC arm accrue costs of established clinical management

Clinical expert comments

- Not everyone receiving current BSC has progressive disease, some are stable

AE: adverse events; AUC: area under the curve; BSC: best supportive care; PD: progressed disease; PF: progression free

Key issue 3: Model structure [3]

ERG comments

- **Heterogeneity of NF1 and PN:** emphasised throughout company submission. Treatment effect modifiers: age, PN volume and number of PN-related morbidities → not captured by current model
- **Health state at start of the model:** people in selumetinib arm start in PFS health state and those in comparator arm start in PD health state. The company clarified that all patients enter the model in a progressive disease health state. However, the model still seems incorrect
- **Progression in BSC arm:**
  - assume BSC arm stay in PD for duration of analysis. Evidence in BSC there are people who do not progress or progress slowly and this is not included in model
  - not including PFS in the BSC arm does not match with the evidence provided by the Natural History study and favours selumetinib
  - agree with the company that in people who progressed, a utility lower than baseline is likely to apply (due to PN progression), but this should also be applied to the selumetinib arm, even though the impact is expected to be minor
  - would like to see PN progression in the model to resolve these potential biases

◉ *What is the natural history of disease with BSC?*
◉ *Is the company AUC model suitable?*

BSC: best supportive care; PD: progressed disease; PFS: progression free survival; PN: plexiform neurofibroma;

Clinical evidence inputs in company model

Input	Evidence Source
Population	SPRINT Phase II Stratum I data [redacted]
Intervention	Selumetinib 25 mg/m^2 BSA, twice daily (approximately every 12 hours), up to a maximum single dose of 50 mg
Comparator	Current clinical management including associated pain medication costs which differ by treatment arm
Treatment response	Selumetinib: A simple annual progression rate (5.6%) was derived from the cumulative probability of progression
Adverse events	Grade ≥3 AEs in SPRINT. Treatments have been selected based on clinical guidance, and costs derived from the BNF.
HRQoL data	Vignette-based time-trade-off (TTO) study for stable and PD health states with age-adjustment over life-time and carer disutility
Mortality	SMR for NF1 patients (2.02) applied equally to both arms
Discontinuation rate	Selumetinib arm based on parametric modelling of TTD data from SPRINT Phase II Stratum I (Weibull)
Model settings	Lifetime horizon (100 years), 3.5% discounting for costs and benefits, half cycle correction

AE: adverse events; BNF: British national formulary; BSA: body surface area; PD: progressed disease; TTD: time to treatment discontinuation; TTO: time trade off

Key issue 4: Modelling of progression [1]

Background

- Progression defined as tumour volume increase from baseline of ≥20% or an increase of ≥20% from best response if a patient had had a PR
- Children receiving selumetinib in the SPRINT trial had a higher probability of PFS over three year follow-up compared with the Natural History study age-matched cohort (84% vs 15%)
- Given only 16% of participants in the SPRINT trial experienced progression during the 3-year follow-up, the company considered the data too immature for extrapolation
- Company used the observed data to estimate an annual progression rate of 5.6% per year
- Once patients reach the age of 18, their tumour size is assumed to stabilise and therefore no progression events are assumed to occur after the age of 18

Expert comments

- Being aged over 18 years of age does not necessarily mean that tumour size will plateau and therefore experience no further disease progression – There are adult studies of NF1 PN underway

NF1: neurofibromatosis type 1; PFS: progression free survival; PN: plexiform neurofibromas; PR: partial response

Key issue 4: Modelling of progression [2]

ERG comments

- Progression assessed using one target PN and up to two non-target PN
- Long-term PFS uncertain due to immaturity of data and limited 3-year follow-up
- Unclear how reflective annual progression probability of 5.6% is over the long-term. Kaplan-Meier curves and fit statistics not presented, so fit of exponential curve to the data available could not be assessed
- Assumption no progression occurs after age of 18 is potentially problematic
  1. would favour selumetinib if some people would progress in clinical practice after the age of 18 (selumetinib arm held at higher utility, all in BSC arm assumed to be progressive)
  2. if it is accepted that no progression occurs after 18, then inclusion of older adolescent patients in SPRINT may bias results. As they would not be expected to progress regardless of treatment
- The company presented data on change in PN volume from the Natural History study, separated by age group in their clarification response. This data shows a substantially lower likelihood of progression from the age of 16.
- It would appear that patients aged 16 and above in SPRINT would be unlikely to progress, regardless of treatment

◉ *Is it clinically plausible that no progression occurs over the age of 18?*
◉ *Would treatment with selumetinib continue beyond the age of 18?*

 BSC: best supportive care; PFS: progression free survival; PN: plexiform neurofibroma

Key issue 5: Utility values [1]

Background [1]

- Company collected patient and carer PedsQL data in SPRINT Phase II Stratum I trial
- EQ-5D utility mapping function for PedsQL available from a study by Khan et al; however company did not use because:
  - derived from 11–15 year olds → limit the applicability to younger children
  - sample of children were not recruited based on having health problems
  - mapping using Khan et.al., may not appropriately reflect utility score of NF1 PN patients in wider age range (3–18 years of age) from the SPRINT trial
- Company base case used Time Trade Off (TTO) interviews with 100 members of the general public, using different health state vignettes, to estimate the health state utility values

TTO study utility values

State	Utility value	Confidence interval
Paediatric patient without selumetinib	[redacted]	[redacted]
Paediatric patient with selumetinib	[redacted]	[redacted]

- Company argue utility values from NICE appraisal of burosumab (HST 8) informative and relatively similar to vignette study:
  - Severe XLH patients utility score = 0.48
  - Mild symptoms utility score = 0.67

NICE

NF1: neurofibromatosis type 1; PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibromas; TTO: time trade off; XLH: X-linked hypophosphataemia

Key issue 5: Utility values [2]

Background [2]

Utility values by PN location

- Utility values were consistent across different PN locations → supports the use of utilities for the health states with an unspecified PN location

PN location	Utility value off-treatment	Utility value on-treatment	Implied treatment effect
Unspecified (base case)	[redacted]	[redacted]	[redacted]
Face	[redacted]	[redacted]	[redacted]
Trunk	[redacted]	[redacted]	[redacted]
Leg	[redacted]	[redacted]	[redacted]

Key issue 5: Utility values [3]

ERG comments utility values

- PedsQL is a widely used measure of youth HRQoL for which a value set is available for the estimation of utilities. PedsQL from the trial could have at least been used to validate utilities produced by the vignette study
- Company argue on-treatment follow-up being 3 years could be considered a limitation. In current model there is no utility progression over time (except for decline due to ageing) and therefore this limitation does not represent a worse option than already modelled
- There is no way of understanding how raw score differences in PedsQL translate into differences in utility → not able to determine appropriateness of the size of the difference in utilities observed in the vignette study using the PedsQL data presented
- TTO valuation fails to meet NICE reference case that HRQoL must be measured/reported in patients → No patient data is involved and cannot be sure how reflective the descriptions or the utilities produced are of the patients in the trial
- The treated vignettes were not validated with patients and carers
- There is no impact of treatment discontinuation on utility unless that discontinuation is associated with progression

◉ *Is it reasonable not to map PedsQL to EQ-5D?*
◉ *Is the company TTO vignette study appropriate to estimate health state utility values?*
◉ *Are the utility estimates appropriate for the disease states?*

HRQoL: health related quality of life; PedsQL: Pediatric Quality of Life Inventory; TTO: time trade off

Key issue 6: Carer disutility [1]

Background:

- Clinical experts advise NF1 PN has impact on QoL of parents/carers. No utility data specific to parents/carers identified. Below assumptions were made in company base-case analysis

Base case assumption	Value in base case	Source
Carer disutility	[redacted]	Same relative decrement as patients
Mean start age of parent/carer	30.6 years	Mean age at childbirth from ONS
Length of caring	Up to patient turns 18	-
Number of carers	1.4	Average UK household size of 2.4

- The clinical experts confirmed that there is a substantial HRQoL impact on parents/carers, through the following:
  - emotional distress, constant worry and anxiety
  - social isolation
  - stress and mental burden associated with providing a range of support
  - disrupted social activities and time off work
- Alternative company scenarios include
  - utility decrement of 0.08 per parent/carer (based on values reported in HST11)
  - vary carer disutility as a proportion of patient disutility (50% or 75%)
  - limiting the duration of carer disutility until patient turns 24 or carers turn 64

NICE HRQoL: health related quality of life; NF1: neurofibromatosis type 1; ONS: office of national statistics; PN: plexiform neurofibromas

Key issue 6: Carer disutility [2]

ERG comments carer disutility

- Assumption that impact of caring is equal to impact of disease is unjustified → carer disutility of [redacted] is higher than those observed in the literature and other NICE appraisals
- In a recent review of NICE appraisals, carer disutilities were identified in 6 TAs and 4 HSTs in paediatric or combined paediatric/adult populations which identified several disutilities associated with caring for children:
  - a disutility of 0.11 for parents of children with Duchenne Muscular Dystrophy (DMD) at a non-ambulatory stage
  - a disutility of 0.07 for carers of children with activity limitations
  - Non-ambulatory DMD patients are unable to walk and have substantial care needs, which would be expected to be greater than those carer needs associated with NF1 PN
  - Does not support a carer disutility of [redacted]
- The ERG would argue that a disutility of 0.07 may be more appropriate. The ERG note that the company incorrectly reported this 0.07 disutility as 0.08
- Unclear if average of 1.4 carers is appropriate → Based on all UK household members except the patient being carers. ERG considers assumption of 1 carer is more appropriate

◉ *Which disutility value is more appropriate? How many carers should it be applied to?*

Key issue 7: Utility waning after progression [1]

Background

- In the BSC arm, HRQoL was assumed to remain constant over time at [redacted]. No further decrements due to events were incorporated.
- The benefit of selumetinib is modelled via improved utility values from baseline to [redacted] within 1 year
- Utility remains constant for patients who maintain partial response or stable disease.
- If people on selumetinib experience substantial PN growth or progression their utility value declines downwards back to baseline, over a period of 5 years

BSC: best supportive care; HRQoL: health related quality of life; PN: plexiform neurofibroma

Key issue 7: Utility waning after progression [2]

ERG comments

- Company assumed linear waning from [redacted] to [redacted] over 5 years post-progression → No supporting evidence for assuming a period of 5 years waning utility
- In model, mean starting age is [redacted] years and people stop treatment at age 18 → 5-year waning represents substantial period of benefit relative to treatment period of [redacted] years
- ERG considers a linear decline in utility over 1 year post-progression more appropriate. This equals the period assumed to obtain full on-treatment utility after treatment initiation
- Additionally, the vignette used to estimate a utility value for progressive state describes the PN growing, and no treatment is received. This already applies at the time of progression
- Stability of utility after 18 years of age, combined with a 5-year post-progression waning can provide a substantial lifetime treatment benefit for which no evidence is presented

◉ Is 5 year or 1 year treatment waning upon progression appropriate?

Key issue 8: Costs not included in the model [1]

Background

- Company base case did not include all relevant costs due to heterogeneity in disease and symptom management → assumed costs in relation to disease management and monitoring will be same in both arms

Costs included in company base case	Clinical expert opinion on type of resource use not included that may be relevant
Selumetinib costs	Clinical nurse specialist support
Treatment-related AE costs (selumetinib arm, patients on treatment only)	Education and psychological support
Pain medication costs	Physiotherapy and occupational therapy
Resource use (MRI) costs (selumetinib arm only)	Clinical appointments for the follow-up and monitoring of treatment with selumetinib
	Use of medication for anxiety and depression in adult patients

- Company indicated that there is no specific data to support a quantitative difference in the symptom management costs other than pain medication costs → decided to exclude majority of these costs for simplicity and to avoid unnecessary uncertainty
- Company indicated that excluding costs for management of PN-associated morbidities was a conservative assumption, since they anticipated a reduction in PN volume would lead to reduced PN-associated morbidity costs in selumetinib arm

Key issue 8: Costs not included in the model [2]

Clinical expert comments

- Anticipate MRI scans every 6 months while having selumetinib, but not been agreed yet
- Frequent hospital visits, at least initially, to monitor treatment and adverse effects

ERG comments

- Limited number of costs included in base-case analysis → does not provide a representative overview of all relevant costs. Although inclusion of additional cost items would require data on resource use in those treated with selumetinib, which is not available
- Company assume 2 additional MRI scans per year based on minimal number indicated by clinical experts. Clinical expert opinion provided to the ERG suggested a frequency of once every three months → assumed additional MRI scans at frequency of 4 times per year.
- Plausible that any relevant disease management costs will be reduced following treatment with selumetinib and agree treatment with selumetinib is likely to reduce management costs, therefore exclusion of these costs may be seen as a reason to interpret the cost-effectiveness results as conservative estimates
- However, inclusion of data on all relevant cost items, for people treated with selumetinib and with BSC, would provide a more comprehensive picture on costs

◉ *How many additional MRI scans would be expected per year while having selumetinib?*
◉ *Are there any other costs that would differ between the 2 treatment arms that have not been included in the model?*

NICE BSC: best supportive care

Cost effectiveness results

Company base case results

Company deterministic and probabilistic cost-effectiveness results, selumetinib versus standard care, includes the PAS price for selumetinib.

Company's base case (deterministic)							
Option	LYGs	QALYs†	Costs†	Inc. LYGs*	Inc. QALYs†	Inc. costs†	ICER
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,169

Company's base case (probabilistic)					
Option	QALYs†	Costs†	Inc. QALYs†	Inc. costs†	ICER
Standard of Care (95% CI)	[redacted]	[redacted]	-	-	-
Selumetinib (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†costs and QALYs discounted at 3.5%

Results of one-way deterministic sensitivity analysis

Variable (lower bound to upper bound)	ICER lower bound	ICER upper bound
Weibull: scale ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]
Utility - Untreated ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]
Discount rate outcomes (1.50% to 6.00%; base case 3.50%)	[redacted]	[redacted]
No. of carers (0.00 to 2.00; base case 1.40)	[redacted]	[redacted]
Utility Age Reg constant (0.761 to 1.141; base case 0.951)	[redacted]	[redacted]
Cumulative probability of progression (5.84% to 26.16%; base case 16.00%)	[redacted]	[redacted]
Utility - Treated ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]
BSA ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]
Discount rate costs (1.50% to 6.00%; base case 3.50%)	[redacted]	[redacted]
BSA Linear regression age coefficient ([redacted] to [redacted]; base case [redacted])	[redacted]	[redacted]

NICE BSA: body surface area

ERG base-case

Cumulative impact of the ERG's preferred model assumptions

Preferred assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)[a]
Company base-case	[redacted]	[redacted]	£93,169
ERG change 1: caregiver disutility equal to -0.07	[redacted]	[redacted]	£117,352
ERG change 2: carer disutility applied to 1 caregiver	[redacted]	[redacted]	£121.278
ERG change 3: waning of utility after progression over 1 year	[redacted]	[redacted]	£133,912
ERG change 4: 4 MRIs per year for selumetinib – ERG base-case	[redacted]	[redacted]	**£134,410**

ERG scenario analyses – treatment duration

Preferred assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)[a]
ERG base-case (8-year treatment duration)	[redacted]	[redacted]	£134,410
No maximum treatment duration	[redacted]	[redacted]	£160,312

[a] ICERs are deterministic including PAS price

NICE Abbreviations: ICER = incremental cost effectiveness ratio; inc = incremental; MRI = magnetic resonance imaging; QALY = quality adjusted life year.

Key issues

Issue	Slide(s)	Impact
1 Long-term clinical effectiveness of selumetinib and BSC	15	
2 • Lack of direct comparison between selumetinib and BSC • Generalisability of SPRINT to UK practice	16-17	
3 Model structure	24-26	
4 Modelling of progression	28-29	
5 Quality of life data and utility values used within the model	30-33	
6 Carer's disutility values used within model and number of carers	34-35	
7 Utility waning after progression	36-37	
8 Costs not included in the model	38-39	

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Number of additional QALYs (X)	Weighting
Less than or equal to 10	1
11 to 29	Between 1 and 3 (equal increments)
Greater or equal to 30	3

Scenario	Incremental QALYs	
	Discounted	Undiscounted
Company base case	[redacted]	[redacted]
ERG's preferred assumptions	[redacted]	[redacted]

No QALY weighting applied in company or ERG base case.

NICE ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Service design and delivery

Company

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

Professional group

- If the NF1 MDT agrees that MEKi is the best treatment option then anticipate this will be delivered and monitored in designated local oncology units

MDT: multidisciplinary team; MEKi: mitogen-activated protein kinase inhibitor; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Innovation

Company:

- **First licensed disease-modifying treatment for NF1 PN**
- **Unmet need**: selumetinib will provide an opportunity to understand the long-term impact of disease-modifying treatment for PN, opening the door for further innovations in the care of patients with symptomatic, inoperable PN
- **Efficacious**: 68% of people in SPRINT Phase II Stratum I experienced a confirmed partial response, defined as ≥20% decrease in PN volume from baseline.
- **Improves social aspects** of disease: benefit patients through improving their ability to perform normal activities of daily living, social functioning and emotional wellbeing

◉ *Does selumetinib represent a step-change in the treatment of inoperable symptomatic NF1 PN?*

NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Equalities

Selumetinib is indicated for use in children aged three years and above

Company

- The use of selumetinib is not expected to raise any equality issues.

Professional group

- Children who are not known to or not referred to the national NF1 service will not be aware of treatment options and could therefore be disadvantaged although knowledge of NF1 is increasing amongst GP's via the work done by the NF charities
- There may be an issue if once eligibility is agreed children are not easily able to access treatment via their local oncology centre and have to travel

Patient group

- Treatment needs to be available to everyone.
- Patients who cannot access the specialist centres should be able to access the treatment
- The use of the treatment should be based on need, there needs to be clear guidance for CCGs to ensure that patients who need the treatment aren't denied on a cost basis
- Treatment offered needs to be equal and should not be based on a person's knowledge, understanding or by their beliefs or religious or ethnic background

◉ *Are there any potential equalities issues that should be considered for selumetinib?*

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

QALY, quality-adjusted life year; QoL, quality of life