NICE National Institute for Health and Care Excellence

Part 1	No confidential information
For public	

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

2nd Evaluation committee meeting
Chair's presentation

Chair: Peter Jackson

Evidence Review Group: Kleijnen Systematic Reviews

Technical team: Nigel Gumbleton, Joanna Richardson, Richard Diaz

Company: AstraZeneca

16th February 2022

Selumetinib, Koselugo®

Marketing authorisation granted June 2021	Treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 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.
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 m^2) – £257,135 (BSA 1.90–1.94 m^2) **An updated confidential patient access scheme has been submitted**

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

Disease background

Cause

- Rare genetic disorder
- Caused by defect in NF1 gene situated at chromosome 17q11.2
- PNs are a neurological manifestation from nerve fascicles that grow along length of nerve
- Most 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

Disease background: treatment pathway

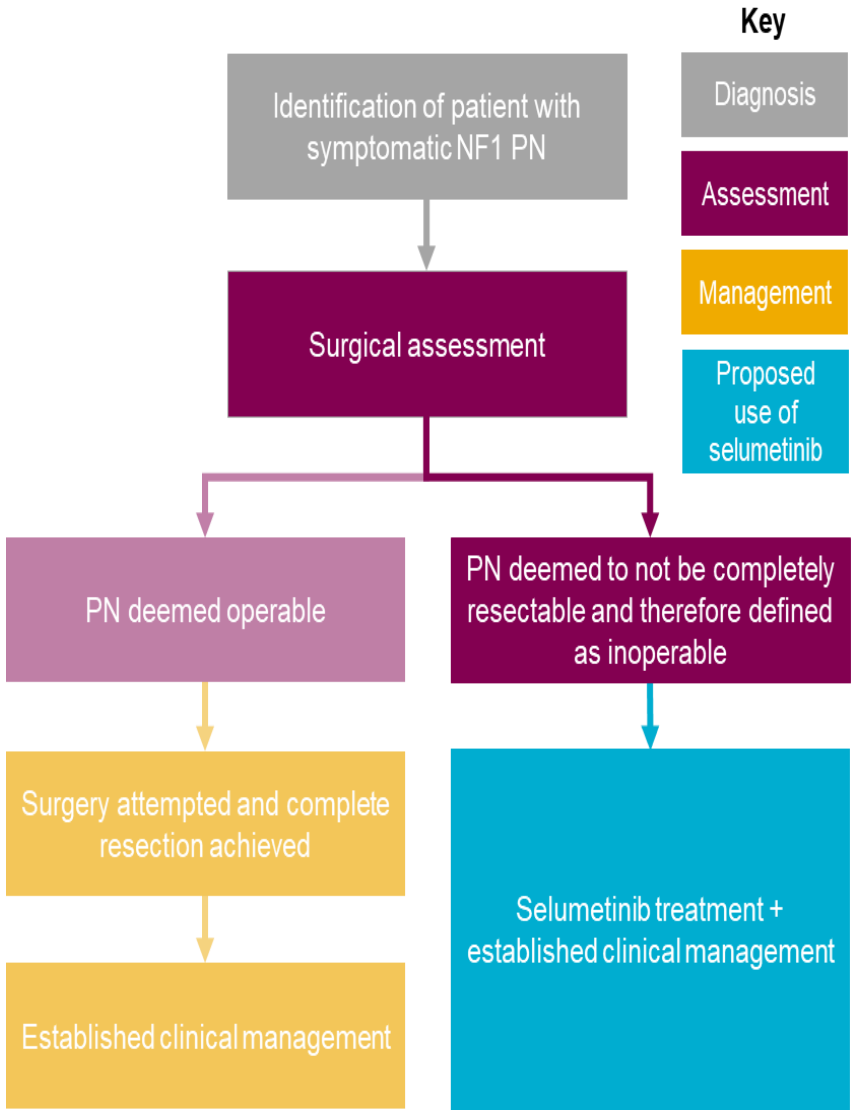
Treatment centres

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
- Surgery only if complete resection achievable
- 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 much-needed pharmacological option for patients with symptomatic PN that are inoperable



ECM1 summary (1/2)

Population	Children aged 3 years and over with symptomatic and inoperable PN associated with NF1
Comparators	Established clinical management without selumetinib, including pain management
Outcomes	

Outcome	Submission	Model
Complete and partial response rate	Yes	Yes
Progression free survival	Yes	Yes
Growth rate of PN	Yes	No
Disfigurement	Yes	No
Physical functioning	Yes	No
Visual function	Yes	No
Airway functioning	Yes	No
Pain	Yes	No
Adverse effects of treatment	Yes	No
Duration of response	Yes	No
Time to progression	Yes	No
Global impression of change	Yes	No

 NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

ECM1 summary (2/2)

Clinical trial	SPRINT Phase II Stratum I, n=50
Trial design	Interventional, single arm, open label
Comparator	Established clinical management without selumetinib, including pain management
Comparator data source	Natural History Study age-matched cohort, n=93
Results	See table below
Model	AUC approach, non-progressed, progressed or deceased states
Committee conclusion	Did not accept model. Could not establish if selumetinib is an effective use of NHS resources without further information

Outcome	SPRINT Phase II Stratum I	Natural History Study age-matched cohort
ORR, %	68	0
Median PFS, years	Not reached	1.3 (1.1 – 1.6)
Probability of PFS at 3 years, %	84%	15%

 AUC: area under the curve; ORR: objective response rate; PFS: progression free survival

ECD conclusions

The committee concluded:

- PN associated with NF1 is a highly heterogenous condition that can affect the body across multiple organ systems and is associated with significant morbidities
- PN associated with NF1 are rare and can substantially affect the lives of people with the condition, their families and carers
- There is lack of knowledge about the condition and many children with NF1 are not known to or attending one of the specialist centres and therefore are not having the correct treatment
- Current treatment options are very limited, involving invasive therapies and often surgery is not able to fully remove the PN
- Treatments are needed for inoperable plexiform neurofibromas
- SPRINT Phase 2 Stratum 1 is generalisable to the UK population

Committee preferences at ECM1

Issue	Committee preference
Model structure	Patient-level model
	Progression-free state for BSC arm
	Progression to happen after age of 18
	Accounts for progressive nature of condition, age and location of PN
	Clinical outcomes important to people with PN, carers and clinicians
Carer disutility	Dependent on PN location and morbidity experienced
	Applied to 1 carer
	In both selumetinib and best supportive care arms
Treatment duration	Possibility for selumetinib treatment to continue after age of 18
Utilities	Values obtained from trial used in analysis either by mapping algorithm or validation of time trade off utilities by mapped utilities
	Utility waning 1 year after progression
Costs	Full resource use costs included for BSC and selumetinib arms

 BSC: best supportive care; PN: plexiform neurofibromas

ECD recommendation

The committee was **minded not to recommend** selumetinib as an option for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over

Further information requested from the company for the 2nd ECM:

- a patient-level model
- utility values obtained from patients in the trial
- carer disutility values dependent on PN location and morbidity
- a breakdown of full resource use costs for selumetinib and best supportive care arms
- the possibility for selumetinib treatment to continue after the age of 18

ECD consultation responses

Consultation comments received from

- Nerve Tumours UK
- Childhood Tumour Trust

Company response

- The company submitted **additional evidence** and a **new economic analysis**
- **Proposed an increased PAS discount**

Summary of consultation comments (1)

Patient organisations

Innovation	
Current treatment	• Exciting that there is a drug treatment available • Surgery has been the main treatment until MEK inhibitors became available. Many PNs cannot be entirely removed by surgery. But surgery can improve function and quality of life.

Treatment decisions	
Treatment centres	• Decision making about who should receive selumetinib should be undertaken by the national neurofibromatosis teams at Guy's Hospital, London and St. Mary's Hospital, Manchester • Treatment could be carried out in conjunction with local centres as this avoids unnecessary disruption to schooling, parents' employment and family life
Criteria	• Clear criteria must be in place • "Inoperable tumour" and "symptomatic" should be clearly defined

Summary of consultation comments (2)

Patient organisations

Treatment duration	
	• Do not know how long the drug should be given for and whether there will be a need for ongoing treatment in adult clinics.

Outcomes	
Quality of life	• Measures that look at effectiveness of treatment should be robust and weight should be given to patient perceived quality of life • It is important to note that although selumetinib can have an impact in the short term on quality of life due to additional tests and hospital visits the long-term overall outcome should improve quality of life for those with plexiform tumours.

"A 20 year old had to have her leg amputated due to an MPNST. (Cancerous Plexiform Tumour) Although she was known to have NF1 from the age of 7, it took 18 months of her mother fighting to get the 'large red and painful lump' looked at. The cancer has now spread to her lungs and no more treatment is available. We don't know if the Selumetinib may have helped this young girl, but the point is she would never have had the opportunity, as by the time she had reached the Highly specialised centres it was too late"

 MPNST: malignant peripheral nerve sheath tumour; NF1: neurofibromatosis type 1

Company post-ECM1 approach

Summary of company post-ECM1 approach

	Updated company base-case	Committee preference
Model Structure	Progression-free state for BSC arm	**Yes**
	Progression to happen after age of 18	**Yes**
Carer disutility	In both selumetinib and best supportive care arms	**Yes**
	Applied to 1.4 carers	**No**
Treatment duration	Selumetinib treatment continue after age of 18	**Yes**
Utilities	Utility waning 3 years after progression	**No**
	Maintain original utilities approach - vignette study	**No**
Additional costs	Full resource use costs included for BSC and selumetinib arms	**Yes**

	New company scenarios	Committee preference
Utilities	Utility waning 1 year after progression	**Yes**

NICE BSC: best supportive care

Key issues for discussion

Key issues

Issue		Slide(s)	Impact
1	Patient level model	18-19	
2	Progression-free state in BSC arm	20-21	
3	Progression after age of 18	22-23	
4	Clinical outcomes in the model	24-28	
5	Carer disutility value	29-30	
6	Carer disutility dependent of PN location and morbidity	31-32	
7	Number of carers	33-34	
8	Treatment after age of 18	35-36	
9	Utility values	37-39	
10	Utility waning after progression	40-41	
11	Full resource use costs	42-45	

Model driver **Unknown impact** **Small impact**

NICE BSC: best supportive care; PN: plexiform neurofibromas

Issue 1: Patient-level model

ECM1: Company preference	ECM1: Committee preference
AUC approach with non-progressed, progressed or deceased states	Patient-level model which accounts for progressive nature of the condition, age, location of PN and outcomes that may have a direct effect on quality of life

Company post-ECM1 approach: original base case maintained

- Available evidence (SPRINT & Natural History study) does not allow patient-level model
- Rare for patient-level models in HST due to limited availability of patient-level data
- Explored regression based patient-level model. NF1 PN heterogeneity and SPRINT small sample size (n=50) → unable to establish quantitative relationship between potential covariates for decision-making purposes. Also unable to establish relationship in BSC because HRQoL/other patient reported outcomes not available from Natural History study
- Covariates explored: age, PN location, PN volume and quality of life → Could not establish correlation between PedsQL and treatment effect modifiers. Likely due to heterogenous nature and complexity of PN location and volume
- Patient-level model would result in higher uncertainty. Larger number of assumptions to be made on quantitative relationship between effect modifiers and outcomes
- Current approach is most robust, given data available and heterogeneity of NF1 PN

No change from ECM1

AUC: area under the curve; BSC: best supportive care; HRQoL: health related quality of life; NF1: neurofibromatosis type 1; PedsQL: Paediatric Quality of Life Inventory; PN: plexiform neurofibromas

Issue 1: Patient-level model

ERG comments

- Both modelling approaches require assumptions that would not be fully evidence based. ERG unable to determine what approach would be the most appropriate and/or feasible
- ERG does not agree with interpretation of results of regression analyses
- Focused on statistical significance, ERG considers focus should be direction and size of effects. Non-significance may imply wider CI's and increased uncertainty and should not prevent including meaningful associations in cost effectiveness model
- Regression analyses constrained by small data set and disease heterogeneity, but some effects observed, especially when tumour volume explored as predictor for HRQoL
- This association could have been further explored, however, difficult to predict whether results would have changed substantially or not
- Definition of health states in terms of progression is problematic. People in BSC may experience continuous PN growth, even if this might occur at a slow pace for some. It is possible that those with continuous growth might still fall under definition of non-progression
- Clinical experts advised reducing PN volume by 20% may not always result in clinically meaningful improvement. These issues may have been resolved using patient-level model

Is the company AUC model suitable for decision making?

BSC: best supportive care; CI: confidence interval; HRQoL: health related quality of life; PN: plexiform neurofibromas

Issue 2: Progression-free state in BSC arm

ECM1: Company preference	ECM1: Committee preference
Progressed disease state only in BSC arm	PF state in BSC arm, which would better reflect the natural history of the disease

Company post-ECM1 approach: updated base case

- PF state in BSC arm implies same rate of PN growth/volume reduction and QoL as selumetinib in a progression-free state → not accurate or appropriate
- Natural History study = 0 people had PN volume reduction from baseline (15.9% median growth rate per year). Individual PN growth rate varies, trend is for growth over time
- In addition, BSC experience persistent PN growth, even if this growth rate does not meet formal definition of 'progressive disease' used in SPRINT (≥20% increase in PN volume)
- PF state in BSC arm implies BSC with progressive disease and non-progressive disease experience different QoL → no evidence from Natural History study. Without treatment, unlikely to experience improved PN-associated morbidities, regardless of PN growth rate
- Company implemented recommendation from committee to test impact of PF in BSC arm
- BSC arm enter in non-progressive state. However, BSC arm do not experience PN volume reduction or symptom improvement seen with selumetinib treatment → not equivalent utility
- Applied utility score of [redacted] to PF in BSC (midpoint between baseline utility ([redacted]) and utility score of selumetinib arm in PF state ([redacted]) → conservative approach, favours BSC arm and does not reflect the experience of patients in the SPRINT

Progression free state included in BSC arm

BSC: best supportive care; PF: progression free; PN: plexiform neurofibromas; QoL: quality of life

Issue 2: Progression-free state in BSC arm

ERG comments

- Evidence supports PF state in BSC → [redacted]% in SPRINT had non-progressive PN at baseline. In the Natural History age-matched cohort, at 3 years, 15% remained PF
- ERG prefer an individual patient model, but inclusion of PF state in BSC is at least more realistic than assuming all patients have progressed from the outset
- When health states defined in terms of progression, inappropriate to assume different utilities per treatment arm for same health state
- If HRQoL were modelled on PN volume, difference in HRQoL between selumetinib and BSC would be obtained, even if both were in PF state, it is expected that PN volume in selumetinib patients would decline while BSC patients experience continuous tumour growth. Since the model cannot capture this, the same utility should be used for PF state, even if this might be conservative
- Lognormal used to model PF state in BSC arm. No further details were provided, therefore, ERG cannot assess appropriateness. Other options explored in scenario analyses
- In revised model, company included PF state in BSC arm following full parametric modelling as suggested by ERG. Selumetinib arm remains unchanged → inconsistent with approach taken in BSC arm of the model
- In AUC model, selumetinib arm stay PF longer than BSC. Original utilities associated with progression and PF ([redacted] and [redacted], respectively) were assumed in revised ERG base case

Which method for including progression-free state in BSC is preferred?

AUC: area under the curve; BSC: best supportive care; HRQoL: health related quality of life; PF: progression free; PN: plexiform neurofibromas

Issue 3: Progression after age of 18

ECM1: Company preference	ECM1: Committee preference
Once people reach the age of 18, PN size stabilises and no progression events happen after this age	Model should allow progression to happen after the age of 18 years

Company post-ECM1 approach: updated base case

- Natural History study = 0.7% median PN growth rate per year in people ≥18 years. Significant contrast with 14.6% median PN growth rate per year in people <18 years, and substantially lower than ≥20% increase used to define progressive disease
- Small potential of progression ≥18 years, revised model to allow progression after age 18
- Applied annual progression rate of [redacted] for both arms after age of 18
- Natural History age matched cohort = [redacted] of patients experienced tumour progression over [redacted] years (equates to [redacted]/year). As paediatrics experience tumour growth rate [redacted] times higher than adults (14.6%/year versus 0.7%/year), used simple calculation of [redacted] to derive progression rate of [redacted] for people aged >18 years
- PN growth rate even lower in older adults, therefore model assumes any further PN progression would stop by age of 24, in both the selumetinib and BSC arms
- In acknowledgement of potential remaining uncertainties, company have used conservative parameters ([redacted] instead of [redacted] as progression rate for people aged ≥18 years

Possible for progression to occur after 18 and up to 24 years of age

Issue 3: Progression after age of 18

ERG comments

- ERG agrees in general with the approach taken by the company
- Some of company assumptions seem arbitrary and/or unclear
- Alternative assumptions provided by the ERG exploring the impact of the age at which PN progression stops
- Scenarios include PN progression stopping at 18, 30, 40, 50 years and no stopping

Is the company rate of progression after the age of 18 appropriate?
At what age is it preferred to assume no further progression occurs after?

Issue 4: Clinical outcomes in the model

ECM1: Company preference	ECM1: Committee preference
Include disease progression (representing change in PN volume) as a main driver of the model	Include clinical outcomes that are important to people with PN, carers and clinicians in the model. Such as pain, which were felt to be more important than PN volume reduction

Company post-ECM1 approach: original base-case maintained

- Explored including clinical outcomes in the model. Challenges included that very few people in SPRINT had each type of morbidity at baseline (e.g. 52% reported pain at baseline) and people often experience multiple morbidities due to PN in multiple locations
- Not feasible to correlate changes in quality of life with specific morbidities. Also challenging if other effect modifiers considered (PN size, location, growth rate and age)
- Heterogeneity of size and location of PN and associated morbidities make quantitative relationship between PN volume and clinical outcomes difficult to define
- Relationship between PN volume reduction and clinical outcomes was evaluated in SPRINT. Correlation between PedsQL and PN volume, NRS-11 pain scores show in most cases volume reduction is linked to improvements in HRQoL or pain
- PN volume change related to improvements in clinical outcomes such as pain and QoL. Absolute amounts of volume reduction cannot be correlated to degree of symptom improvement. Overall trend for improved QoL and pain outcomes with reduced PN volume

No change from ECM1

HRQoL: health related quality of life; NRS-11: Numerical Rating Scale-11; PedsQL: Paediatric Quality of Life Inventory; PN: plexiform neurofibromas; QoL: quality of life

Issue 4: Clinical outcomes in the model

ERG comments

- Including additional clinical outcomes (e.g., pain) in the model was deemed infeasible by the company
- ERG acknowledges the limitations of the data, however, the largest effect on PedsQL seemed to be of normalised tumour volume (Key issue 1), with which there might have also been a clearer correlation with pain

Is the current modelling approach used by the company, based on disease progression (representing change in PN volume) appropriate?

Issue 5: Carer disutility value

ECM1: Company preference	ECM1: Committee preference
Carer disutility value of [redacted], only in BSC arm	Carer disutility value of 0.07, in both BSC and selumetinib arms

Company post-ECM1 approach: updated base case

- NF1 PN has significant negative impact on emotional and social wellbeing
- People with NF1 PN may experience bullying, stigma or social exclusion
- Carers report burden of patient care, communicating with others regarding their child's condition and emotional impact of NF1 PN
- Likely the 0.07 utility decrement for carers does not fully reflect burden for carers. Company maintain carer disutility of [redacted] reflects carer burden of people having BSC
- Acknowledge committee preference to include caregiver disutility in selumetinib arm. Should reflect impact of effective disease control with selumetinib when compared to BSC
- Company base case includes carer disutility of [redacted] in selumetinib arm. Represents a reasonable point between disutility applied in BSC arm ([redacted]) and the committee preferred value (0.07)
- The absolute difference in carer disutility between 2 treatment arms is [redacted], which reflects impact of disease control with selumetinib on carer QoL

Carer disutility in both arms – Absolute difference of [redacted]

 BSC: best supportive care; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas; QoL: quality of life

Issue 5: Carer disutility value

Technical team comments

- 2019 DSU report includes carer disutility values used in previous NICE appraisals

TA/HST	Population	Size of carer QoL effect
TA217	Alzheimer's disease	Utility ranged from 0.85 – 0.94
TA127, TA254, TA312, TA303, TA320, TA533. TA527	Multiple sclerosis	Disutility ranged from 0.00 – 0.14 depending on the health state the patient was in
TA493	Multiple sclerosis	Disutility ranged from 0.002 – 0.173
TA373	Juvenile idiopathic arthritis	Disutility ranged from 0.02 – 0.07
HST2	Mucopolysaccharidosis type IVa	Disutility ranged from 0.00 – 0.14
HST3	Duchenne muscular dystrophy	Disutility of 0.11
HST7	SCID	Family QALY loss of 9% of child's QALY loss
HST8	X-linked hypophosphataemia	Disutility of 0.07

ADD-SCID: Adenosine deaminase deficiency–severe combined immunodeficiency

Issue 5: Carer disutility value

ERG comments

- ERG considers there is no supporting evidence to assume a caregiver disutility of [redacted]
- ERG still prefers a caregiver disutility of 0.07 which was used in HST8 Burosumab
- However, the ERG acknowledges that improvement in disease control with selumetinib compared to BSC should be considered in the model and thus applying a lower caregiver disutility value in the selumetinib arm seems reasonable, even though, in the absence of data, its value was arbitrarily assumed
- Alternative assumptions provided by the ERG exploring different carer disutility values in additional scenario analyses
- Scenarios include: 75% and 50% relative difference, disutility of 0.07 applied to 1.4 carers, disutility of [redacted] applied to 1.4 carers, disutility of [redacted] applied to 1 carer

Which carer disutility values and absolute difference in carer disutility between 2 treatment arms is preferred?

Issue 6: Carer disutility dependent on PN location and morbidity

ECM1: Company preference	ECM1: Committee preference
Carer disutility values not dependent on location and morbidity	Carer disutility values dependent on PN location and morbidity experienced

Company post-ECM1 approach: original base-case maintained

- Estimating carer QoL based on a respective PN location and associated morbidity faces similar challenges as estimation of patient QoL by PN location or morbidity
- All people in SPRINT had PN-related symptoms at baseline. However, considerable heterogeneity in symptoms observed and related severity. People in SPRINT had an average of 3 different target PN morbidities. Similarly, 23% of PN were associated with 2 morbidities and 10% of PN were associated with 3 or 4 morbidities at baseline
- Therefore, unfeasible to derive specific impact of single locations/morbidities and, in particular, account for likely interplay of different combinations of morbidities
- Carer disutility should be equally applied independent of specific PN locations/morbidities

No change from ECM1

Issue 6: Carer disutility dependent on PN location and morbidity

ERG comments

- Developing a patient-level model accounting for progressive nature of NF1, age and location of PN's, and including clinical outcomes that are important to people with PN, carers and clinicians (such as pain), was deemed unfeasible by the company, given the limitations of the available data
- These limitations also prevented the company from estimating caregiver utility decrement values dependent on PN location and morbidity

Is it appropriate to apply carer disutility equally independent of specific PN locations/morbidities?

NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Issue 7: Number of carers

ECM1: Company preference	ECM1: Committee preference
Carer disutility value applied to 1.4 carers	Carer disutility values applied to 1 carer

Company post-ECM1 approach: original base-case maintained

- Patient and carer expert feedback supports assumption that care for a patient with NF1 PN is likely to place a burden on entire family
- In addition, patient experts emphasised that impact of NF1 PN is on the whole family, which can include parents and siblings
- Company maintain original submitted approach of applying carer disutility to 1.4 people → based on average UK household size being 2.4 people and one person being the patient

No change from ECM1

Issue 7: Number of carers

Technical team comments

- 2019 DSU report – most TA and HST considered the health impact on 1 carer only, some have more than 1

TA/HST	Number of carers
HST3 – Duchenne muscular dystrophy	Between 2 and 3
TA386 – Myelofibrosis	1.76 for 57.48% of people
HST7 - Adenosine deaminase deficiency–severe combined Immunodeficiency	Family with unspecified number of members

ERG comments

- Even if it is reasonable that the burden of NF1 PN is to some extent on the whole family (including for example, other children), the ERG still considers that the assumption of 1 caregiver is more appropriate
- Not everyone in the household is a caregiver and in the model caregiver disutility is what is being included
- Alternative assumptions provided by the ERG exploring the impact of the number of carers
- Scenarios include 1 and 1.4 carers

How many carers should the disutility apply to?

NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Issue 8: Treatment after 18 years of age

ECM1: Company preference	ECM1: Committee preference
Selumetinib treatment stops at age of 18 years	Possibility for selumetinib treatment to continue after age of 18 years be included within the model

Company post-ECM1 approach: updated base case

- Selumetinib MA states it is indicated for paediatric patients aged 3 years and above, and there are limited data in people older than 18 years. Therefore continued treatment in adulthood should be based on benefits and risks. Where there is continued benefit of selumetinib treatment after age of 18 years, selumetinib treatment could be continued
- Number of adults with NF1 PN who experience progression after age of 18 years is negligible → expect that most, if not all would discontinue treatment when reach adulthood
- Revised model allows disease progression after age of 18 (see key issue 3)
- Company modelled people who started selumetinib at age 10 and continued until age 18 → Assumed [redacted] stop treatment when they reach adulthood; remaining [redacted] would continue treatment into adulthood
- Company assume [redacted] would stop treatment when reach adulthood, and remaining [redacted] would continue treatment based on Weibull curve for time-to-discontinuation
- In acknowledgement of potential remaining uncertainties, company have used conservative parameters ([redacted] instead of [redacted] stopping treatment when reach adulthood) in the model

Possible to continue selumetinib after 18 years of age

NICE

MA: marketing authorisation; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas

Issue 8: Treatment after 18 years of age

ERG comments

- ERG agrees in general with the approach taken by the company although some of the assumptions described above seem arbitrary and /or unclear
- Alternative assumptions provided by the ERG exploring the impact of treatment discontinuation rates after 18 years
- Scenarios include [redacted], [redacted] and [redacted]

What % of people who continue treatment after 18 is preferred?

Issue 9: Utility values

ECM1: Company preference	ECM1: Committee preference
Utility scores from the performed vignette study used in the analysis	Attempt at mapping and direct utility data from trial included. At very least, mapped values used to validate time trade off values

Company post-ECM1 approach: original base-case maintained

- Similar issues mapping PedsQL to EQ-5D, limited number of validated algorithms for mapping of PedsQL to CHU9D: Lambe et al, Mpundu-Kaambwa et al. and Sweeney et al
- All raised similar limitations regarding development and/or validation of such algorithms, such as poor performance for certain age groups or severe disease and low quality of life
- When mapping algorithms applied to baseline PedsQL data obtained from SPRINT, resulting utility value was unrealistically high

Mapping algorithm	Generated utility score, median (range)
Lambe et al	[redacted]
Mpundu-Kaambwa et al	[redacted]
Sweeney et al	[redacted]

- Mapping PedsQL from SPRINT into CHU9D would not appropriately reflect patient utility scores or take account of the full evidence from SPRINT PedsQL data
- Company maintain utility scores from vignette study a more appropriate option = [redacted] without selumetinib and [redacted] with selumetinib

NICE

CHU9D: Child Health Utility 9D; PedsQL: Paediatric Quality of Life Inventory

Issue 9: Utility values

Company post-ECM1 approach: original base-case maintained

- Previous NICE appraisals of orphan drugs that faced similar challenges regarding collection of suitable utility data

Topic	Summary of utilities
TA588 – Nusinersen for spinal muscular atrophy	Committee noted identifying robust utility values in babies and young children is challenging. Final analysis based on utilities generated by company from clinical advisers.
HST6 – Asfotase alfa in paediatric-onset hypophosphatasia	Included utilities estimated by 9 clinical experts as part of a vignette study
HST8 – Burosumab in X-linked hypophosphataemia	Included utilities obtained from dedicated vignette study
HST12 – Cerliponase alfa in neuronal ceroid lipofuscinosis	Committee would generally prefer to include utilities from trials, however acknowledged PedsQL from the trials may not be realistic and considered EQ-5D from the company provided vignette study instead.

No change from ECM1

NICE PedsQL: Paediatric Quality of Life Inventory

Issue 9: Utility values

ERG comments

- ERG considers that the concerns regarding the TTO study presented by the company have not been resolved
- 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
- Agree with the company that their approach is in line with several previous NICE appraisals
- However, that the approaches could be the same, does not imply that the concerns and limitations of particular studies are different
- ERG unable to determine if the TTO utility estimates used by the company are appropriate for decision making or not

Are the utility values from the company TTO vignette study suitable for decision making?

TTO: time trade off

Issue 10: Utility waning after progression

ECM1: Company preference	ECM1: Committee preference
5 years of utility waning	1 year utility waning

Company post-ECM1 approach: updated base case

- When considering decline in QoL following selumetinib discontinuation, important to account for preventative nature of treatment with selumetinib
- People with untreated NF1 PN experience continuous PN growth. Majority of people with NF1 PN treated with selumetinib experience some tumour reduction → difference in tumour volume is expected to steadily increase for entire period of treatment with selumetinib. Importantly, this difference would also be reflected in the associated burden
- Propensity score analyses demonstrated a mean difference in annual PN growth rate between untreated patients from Natural History Study and treated patients from SPRINT
- Therefore, people who experience PN growth following discontinuation of selumetinib, PN would be smaller and less of a burden. This residual benefit on QoL can be expected to persist long term
- Company adjusted model base case to apply a reduced duration of utility waning of 3 years. Also provided scenario analysis based on decreasing duration of utility waning to a minimum of 1 year

3-year utility waning after progression

NICE

NF1: neurofibromatosis type 1; PN: plexiform neurofibromas; QoL: quality of life

Issue 10: Utility waning after progression

ERG comments

- ERG still prefers a linear decline in utility over 1 year after progression as this equals the period assumed to obtain the full on-treatment utility after treatment initiation
- Alternative assumptions provided by the ERG exploring the impact utility waning after progression
- Scenarios include 2 and 3 years to achieve treatment utility after initiating treatment; 2, 3 and 5 years for utility to revert to baseline after progression; no waning; and age-adjusted utility not included

What duration of utility waning after progression is preferred?

Issue 11: Full resource use costs

ECM1: Company preference	ECM1: Committee preference
Only includes costs for selumetinib, adverse event costs, pain medication costs and MRI costs	Analyses with full resource use costs included for both arms of the model

Company post-ECM1 approach: updated base case

- Additional costs have been included within the model
- Most being additional monitoring costs for selumetinib treatment
- NF1 PN requires regular monitoring to check disease status and those treated with selumetinib would need additional monitoring before starting and during treatment
- Types and frequency of monitoring collected from a clinical expert and calculated the corresponding cost
- Did not assume potential cost savings from symptom improvement due to treatment with selumetinib due to lack of quantitative data. As such, this can be considered a conservative approach

Full resource use costs included

Issue 11: Full resource use costs

Additional monitoring costs (baseline to Year 1)

Monitoring	£ per unit	BSC		Selumetinib on treatment		Selumetinib off treatment	
		Number per year	£ per year	Number per year	£ per year	Number per year	£ per year
Physical/skin exam	£587.96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X-ray of left wrist and tibial growth plate	£32.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ophthalmology testing	£28.35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECG/Echo	£91.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood test	£2.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	-	-	[redacted]	-	[redacted]	-	[redacted]

NICE BSC: best supportive care; ECG: echocardiogram

Issue 11: Full resource use costs

Additional monitoring costs (from Year 2)

Monitoring	£ per unit	BSC		Selumetinib on treatment		Selumetinib off treatment	
		Number per year	£ per year	Number per year	£ per year	Number per year	£ per year
Physical/skin exam	£587.96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X-ray of left wrist and tibial growth plate	£32.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ophthalmology testing	£28.35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECG/Echo	£91.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood test	£2.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	-	-	[redacted]	-	[redacted]	-	[redacted]

NICE BSC: best supportive care; ECG: echocardiogram

Issue 11: Full resource use costs

ERG comments

- Company followed committee's recommendation and added additional cost items to the model and compared them across both treatment arms
- Based on feedback obtained from a clinical expert consulted by the company. Details of the communication between the company and the clinical experts were not provided
- Sources for the unit costs were also not provided
- ERG cannot assess whether the additional monitoring costs considered by the company are appropriate or not
- The company also state that potential cost savings from symptom improvement due to treatment with selumetinib were not included in the analyses due to lack of data and considered this as a very conservative approach
- Given the lack of data, the validity of the resource use assumed by the company and whether the approach is conservative can only be assessed by committee and clinical experts

Are the resource use costs in both arms provided by the company suitable?

Other issues

Issue	Company comments	ERG comments
MRI scans	Company already used two additional MRIs in its base case, therefore no update to the model needed. However, company emphasise 2 additional MRIs can be considered a conservative assumption.	The company followed the committee's recommendation and assumed two additional MRI scans for the selumetinib arm of the model. Whether this can be deemed as a conservative approach or not is left to the judgement of the committee and clinical experts

Company base case: Deterministic cost-effectiveness results vs BSC with new proposed PAS

Summary of model revisions (cumulative impact of company revised assumptions and revised base case)

Scenarios included	Key issue	Scenario	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
1	11	Full resource use costs for both arms	[redacted]	[redacted]	£70,888
1, 2	10	+ 3-year waning to baseline utility	[redacted]	[redacted]	£74,113
1, 2, 4	8	+ treatment after 18 years	[redacted]	[redacted]	£76,544
1, 2, 4, 5	3	+ progression after 18 years	[redacted]	[redacted]	£81,141
1, 2, 4-6	2	+ inclusion of PFS in BSC arm	[redacted]	[redacted]	£87,246
1, 2, 4-7	5 & 7	+ carer disutility of [redacted] applied to 1.4 carer	[redacted]	[redacted]	£99,827

Revised company base case

NICE BSC: best supportive care; ICER: incremental cost effectiveness ratio; PAS: patient access scheme; PFS: progression free survival; QALY: quality adjusted life year

ERG revised base-case with new proposed PAS (deterministic)

Individual impact of all committee's preferred assumptions at ECM1

Additional changes	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Revised company base-case	[redacted]	[redacted]	£99,827
Errors corrected	[redacted]	[redacted]	£99,771
Utility waning 1 year	[redacted]	[redacted]	£101,415
Carer disutility 0.07 in BSC, 0.035 in selumetinib	[redacted]	[redacted]	£116,027
Number of carers equal to 1	[redacted]	[redacted]	£105,863
PF state utility equal in selumetinib and BSC	[redacted]	[redacted]	£103,647

Cumulative impact of all committee's preferred assumptions at ECM1

Additional changes	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Revised company base-case	[redacted]	[redacted]	£99,827
Errors corrected	[redacted]	[redacted]	£99,771
Utility waning 1 year	[redacted]	[redacted]	£101,415
Carer disutility 0.07 in BSC, 0.035 in selumetinib	[redacted]	[redacted]	£118,256
Number of carers equal to 1	[redacted]	[redacted]	£120,763
PF state utility equal in selumetinib and BSC	[redacted]	[redacted]	£126,488

Revised ERG base case

NICE

BSC: best supportive care; ICER: incremental cost effectiveness ratio; PF: progression-free; QALY: quality adjusted life year

ERG scenario analysis (deterministic)

Age at which PN progression stops

Assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
18	[redacted]	[redacted]	£120,272
30	[redacted]	[redacted]	£141,050
40	[redacted]	[redacted]	£163,250
50	[redacted]	[redacted]	£177,436
No stop (100 years assumed)	[redacted]	[redacted]	£188,794

NICE

ICER: incremental cost effectiveness ratio

ERG scenario analyses (deterministic)

Parent/carer utility

Scenario	Assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Parent/carer disutility	Relative difference 75% (untreated patient)	[redacted]	[redacted]	£116,981
	Relative difference 50% (untreated patient)	[redacted]	[redacted]	£122,130
	Impact for duration parent/carer lifetime	[redacted]	[redacted]	£113,127
	Disutility of 0.07 for 1.4 carers	[redacted]	[redacted]	£123,741
	Relative impact on carers equal to relative impact on patients (patients = [redacted]) for 1.4 carers (company base case)	[redacted]	[redacted]	£105,423
	Relative impact on carers equal to relative impact on patients (patients = [redacted]) for 1 carer	[redacted]	[redacted]	£112,247

NICE

ICER: incremental cost effectiveness ratio

ERG scenario analysis (deterministic)

Treatment discontinuation rates after 18 years

Assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	£122,324
[redacted]	[redacted]	[redacted]	£132,735
[redacted]	[redacted]	[redacted]	£143,145

NICE

ICER: incremental cost effectiveness ratio

ERG scenario analyses (deterministic)

Utility change over time

Scenario	Assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Utility change over time	2 years to achieve treated HRQoL after initiating treatment	[redacted]	[redacted]	£129,546
	3 years to achieve treated HRQoL after initiating treatment	[redacted]	[redacted]	£133,243
	2 years to revert to baseline HRQoL after progression	[redacted]	[redacted]	£125,186
	3 years to revert to baseline HRQoL after progression	[redacted]	[redacted]	£123,941
	5 years to revert to baseline HRQoL after progression	[redacted]	[redacted]	£121,607
	No waning over time (100 years assumed)	[redacted]	[redacted]	£90,490
	Age-adjusted utility not included	[redacted]	[redacted]	£116,009

NICE

HRQoL: health related quality of life; ICER: incremental cost effectiveness ratio

ERG scenario analyses (deterministic)

Scenario	Assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Selumetinib PF – cumulative probability of progression by year 3	[redacted]	[redacted]	[redacted]	£96,156
	[redacted]	[redacted]	[redacted]	£171,994
Patient utility	Upper CI bound for untreated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	£180,639
	Lower CI bound for treated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	£151,349
	Lower CI bound for untreated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	£97,624
	Upper CI bound for treated utility ([redacted]) (implied TE = [redacted])	[redacted]	[redacted]	£108,643
	PFS utility in BSC arm equal to [redacted]	[redacted]	[redacted]	£120,763

NICE

BSC: best supportive care; CI: confidence interval; ICER: incremental cost effectiveness ratio; PF: progression free; QALY: quality adjusted life year; TE = treatment effect

ERG scenario analysis (deterministic)

BSC PF state – alternative parametric distributions

Assumption	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Exponential	[redacted]	[redacted]	£127,533
Generalised gamma	[redacted]	[redacted]	£131,468
Gompertz	[redacted]	[redacted]	£123,613
Loglogistic	[redacted]	[redacted]	£127,681
Weibull	[redacted]	[redacted]	£123,559
Simple probability	[redacted]	[redacted]	£122,544

BSC: best supportive care; ICER: incremental cost effectiveness ratio; PF: progression free

QALY weighting

- ICER greater than £100,000 per QALY, judgements take account of the **magnitude of benefit** and the additional **QALY weight** that would be needed to support recommendation
- 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	
Compared with BSC	Discounted	Undiscounted
Company base case	[redacted]	[redacted]
ERG's preferred assumptions	[redacted]	[redacted]

NICE BSC: best supportive care; QALY: quality adjusted life year

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 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