National Institute for Health and Care Excellence

Health Technology Evaluation

Mirdametinib for treating symptomatic inoperable plexiform neurofibromas in people 2 years and over with neurofibromatosis type 1 [ID6618]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Company	No comments.	Comment noted. Thank you.
	British Paediatric Neurology Association	Yes this is appropriate due to unmet need.	Comment noted. Thank you.
	Association of British Neurologists	The HS technology evaluation is appropriate – this is the same as for selumetinib in treating paediatric symptomatic plexiform.	Comment noted. Thank you. The routing of this topic was discussed by NICE's Prioritisation Board. It was considered that this topic would be routed as a single technology appraisal.

Section	Stakeholder	Comments [sic]	Action
	Nerve Tumours UK	We consider it is appropriate that you should evaluate this topic, by using a highly specialised technology evaluation.	Comment noted. Thank you. The routing of this topic was discussed by NICE's Prioritisation Board meeting. It was considered that this topic would be routed as a single technology appraisal.
	Childhood Tumour Trust	We're not experts in NICE processes, but we understand that there are several ways medicines can be reviewed. From our perspective, the Single Technology Appraisal (STA) is the most appropriate route for this new drug. There is already one medicine available for children with NF1 and plexiform neurofibromas, but it is only licensed for paediatric use. This new treatment could benefit a wider group, including adults, where there is a significant unmet need. While NF1 itself is not extremely rare, the complication of developing a plexiform neurofibroma affects around 30–50% of people with NF1, highlighting just how many individuals could potentially benefit from improved treatment options. Because this is a single new drug for a single condition, it makes sense for it to be assessed on its own rather than through a broader, more complex process. NF1 is rare, but not so rare that it requires a Highly Specialised Technology evaluation.	Comment noted. Thank you. The routing of this topic was discussed by NICE's Prioritisation Board meeting. It was considered that this topic would be routed as a single technology appraisal.
Wording	Company	Wording is appropriate.	Comment noted. Thank you.
	British Paediatric	Yes. In the draft scope the remit is clear.	Comment noted. Thank you.

Section	Stakeholder	Comments [sic]	Action
	Neurology Association		
	Association of British Neurologists	Reasonable to consider QALYs in determining cost-effectiveness.	Comment noted. Thank you.
	Nerve Tumours UK	The remit is appropriate, but further clarification is needed, for example the definition of symptomatic, inoperable plexiform neurofibroma.	Comment noted. Thank you. The scope remit has not been updated. The definition of symptomatic, inoperable plexiform NF will form part of the evaluation.
	Childhood Tumour Trust	The remit appears to reflect the cost benefit analysis of the technology's effectiveness vs financial considerations. However, the remit might also consider the access to the technology, if approved, as this has potentially impacted on cost vs benefit of other comparative medications.	Comment noted. Thank you. The scope remit has not been updated. The definition of symptomatic, inoperable plexiform NF will form part of the evaluation.
Additional comments on the draft remit	Company	Timing issues: There are NF1 patient populations who are currently not treated with available options, and these are adult patients, paediatric patients between 2-3 years, and patients with swallowing issues.	Comment noted. Thank you. This topic has been scheduled into NICE's work programme.

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	British Paediatric Neurology Association	Timing issues: This medication is already available in the US and EU. There is currently no paediatric formulation of a MEK inhibitor available in the UK and this some children are being denied treatment at a young age when they are most likely to benefit due to potential for rapid growth of their PN.	Comment noted. Thank you. This topic has been scheduled into NICE's work programme.
	Association of British Neurologists	Timing issues: The evaluation is particularly relevant and timely with respect to the adult population as there is no currently available drug treatment option for treating inoperable symptomatic plexiform in adults.	Comment noted. Thank you. This topic has been scheduled into NICE's work programme.
	Nerve Tumours UK	Timing issues: There is currently no treatment available for adults, children under the age of 3 years, or people who cannot swallow tablets, who have a symptomatic inoperable plexiform neurofibroma. This is required urgently to ensure equity of care. The remit should fully define and describe a symptomatic, inoperable plexiform neurofibroma: - persistent pain that is not treatable by standard pain alleviation methods - disfigurement - functional impairment	Comment noted. Thank you. This topic has been scheduled into NICE's work programme. The scope remit has not been updated. The definition of symptomatic, inoperable plexiform NF will form part of the evaluation.

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		- significant risk to function, for example a neurofibroma near the spinal cord, in which a very small increase in the size of the neurofibroma may cause significant impairment - inoperable – neurofibroma too close to vital organs / structures or surgery would cause unacceptable morbidity – e.g. pain or functional impairment that adversely impacts on quality of life The remit does not address issues surrounding pregnancy and conception.	
	Childhood Tumour Trust	Timing issues: This evaluation is of high urgency due to the progressive burden of plexiform neurofibromas, and the substantial impact on education, employment, and relationships. A new therapy could significantly improve quality of life, reduce reliance on NHS and mental health services, and help people return to or remain in work, underscoring the need for timely guidance and implementation. In addition, the cost implication of repeated surgeries only increases as time without technologies being commissioned to offer alternative pathways. Although I am not a clinical professional, I represent the lived experience of more than 2,300 members within our NF1 community, which includes families who have received alternative treatments to this technology and those who have been denied such medical interventions. I have supported my responses with research wherever possible, but the foundation of my contribution comes directly from those with lived experience, whose voices, needs, and concerns I am committed to representing throughout this process, therefore my statistics may need to be confirmed. There is also very limited	Comment noted. Thank you. This topic has been scheduled into NICE's work programme.

Section	Stakeholder	Comments [sic]	Action
		data available on exact figures and therefore everything I say is an estimate based on data I have been able to find.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company	The information provided is accurate and we would like to suggest the following: Paragraph 1: Add that, “Individuals with NF1 have an increased risk of malignancy and shorter life expectancy than the general population (Gutmann et al. 2017, Saleh et al. 2023).” Paragraph 2, sentence 3: Add that PNs can also cause neuropathy, bone destruction, and impaired physical functioning. Paragraph 2, sentence 5: Where it is stated that “PNs are diagnosed in early childhood, grow most rapidly during this period”, add that “PNs can continue to grow into adolescence and adulthood (Jensen et al. 2019).” Paragraph 2, sentence 6: Revise the percent of people with NF1-PN who have inoperable PN to 35% (Ejerskov et al. 2023)	Comment noted. Thank you. The background on the scope is intended to provide a brief overview of the topic being considered. The following background information has been updated and now reads: ‘Most PNs are diagnosed in early childhood and grow most rapidly during this period. But they can continue to grow in adolescence and early adulthood’. Thank you for providing the revised estimate of the percentage of people with NF1-PN who have inoperable PN. The

Section	Consultee/ Commentator	Comments [sic]	Action
			scope has been updated and now reads "Approximately 30% to 50% of all people with NF1 PN have inoperable PN…"
	British Paediatric Neurology Association	The wording in the background section needs to be modified. Neurofibromatosis 1 (NF) is a common genetic condition affecting approximately 25,000 people in the UK [2]. It is caused by a mutation in the NF1 gene located on chromosome 17 and affects multiple body systems. The NF1 gene is important for controlling tumour growth. NF1 is an incurable condition with highly-variable symptoms, including cutaneous (skin), visual (eyes), neurological (nervous system), blood vessels orthopaedic (skeletal) manifestations and can also affect learning and development Plexiform neurofibromas (PNs) are benign nerve sheath tumours that occur in approximately 30 to 50% of people with NF1[5]. They can cause symptoms including pain, motor dysfunction and disfigurement[4] . The location of the PN on the body can impact the severity of the symptoms experienced and the complexity of the condition. Most PNs are diagnosed in early childhood and grow most rapidly during this period. Many symptomatic PN's are inoperable	Comment noted thank you. The background on the scope has not been updated. This is because it is intended to provide a brief overview of the topic being considered and consideration of this and other stakeholder comments indicated the content was accurate.

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		i.e. cannot be completely resected because of their close proximity with important neural and vascular structures.	
	Association of British Neurologists	The background information is broadly accurate, but the estimated prevalence of inoperable plexiform neurofibromas appears higher than we see in real-world clinical practice within the NHS Highly Specialised Services (HSS) for Complex NF1. Within our own HSS cohort (n=~2800 adults), approximately 17% have had a symptomatic plexiform neurofibroma at some point. However, only a subset of these are truly inoperable after specialist radiological and surgical review. The proportion of inoperable PN in the general NF1 population is likely to be lower than suggested, because: Our HSS cohort is enriched for complex and symptomatic referrals, inflating apparent prevalence. Many cutaneous, subcutaneous or intramuscular PN are amenable to surgery, and should not be categorised as inoperable. Deep, infiltrative plexus PN (e.g., paraspinal, head and neck, pelvic) represent a smaller proportion of the overall PN burden. Not all patients within our geographical catchment with PN are referred to us, meaning HSS numbers tend to over-represent complex cases.	Comment noted. Thank you for noting these estimates. Thank you for highlighting the subgroup of mosaic (segmental) NF1. The following subgroup has been added to the scope which captures this: 'People with neurofibromatosis type 1 according to site of symptomatic inoperable plexiform neurofibromas' The background section of the scope has been updated based upon all the consultation responses. It now reads: "Approximately 30% to 50% of all people with

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		A realistic estimate is that only a minority of all PN in NF1 are both symptomatic and inoperable, and this should be reflected in the background section. Also, A small proportion of people with plexiform neurofibromas have mosaic (segmental) NF1, caused by post-zygotic NF1 mutations resulting in disease manifestations confined to one region or segment of the body. These individuals may present with a single plexiform neurofibroma or a cluster of lesions in a restricted anatomical distribution, without meeting full diagnostic criteria for generalised NF1. Although overall disease burden is usually lower, segmental PN can still be symptomatic and inoperable, and may cause significant functional compromise, pain or disfigurement depending on location. Mosaic/segmental NF1 therefore remains an important subgroup within the population who may be considered for treatments.	NF1 PN have inoperable PN[7] (that is PN which cannot be completely resected without a risk of substantial morbidity because of close proximity to vital structures, invasiveness, or high vascularity). Other estimates suggest this proportion may be lower."
	Nerve Tumours UK	The definition is out of date. It is currently defined as Neurofibromatosis 1 (NF1), Neurofibromatosis 2 (NF2) related Schwannomatosis and non NF2 related Schwannomatosis. NF2 and non NF2 related Schwannomatosis are characterised by schwannomas and not neurofibromas.	Comment noted. Thank you. The scope has been updated and now reads: "There are two forms of NF: type 1 (NF1) and type 2 (NF2; also known as NF2-related Schwannomatosis)"
	Childhood Tumour Trust	While the NICE background notes that most individuals with NF1 will have "mild" symptoms, it also states that around 30 to 50% of people with NF1 will develop a plexiform neurofibroma (PN) and 50% of them will have an inoperable PN. The impact of plexiform neurofibromas varies widely —	Comment noted. Thank you. The background section has not been updated. The

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		ranging from small and asymptomatic tumours to large, complex, or rapidly progressing growths that cause pain, disfigurement, functional impairment, and, in some cases, malignant transformation. This broad spectrum of severity highlights why the term “mild” can be misleading when describing NF1 as a whole. We also acknowledge that the new drug under consideration is intended specifically for symptomatic, inoperable plexiform neurofibromas, and therefore does not apply to everyone with a PN.	background reflects the range of symptoms which are associated with NF1 and PNs.
Population	Company	Population is defined appropriately as it is aligned with the anticipated marketing authorisation	Comment noted. Thank you.
	British Paediatric Neurology Association	See changes in background section above	Comment noted. Thank you. Mirdametinib will be evaluated in line with the population defined in its marketing authorisation for neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas. The population included in the scope reflects the population in the key clinical trial, and the population included in the MHRA marketing authorisation.

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	Association of British Neurologists	Overall, the population is defined appropriately as people with symptomatic, inoperable plexiform neurofibromas associated with NF1, which reflects the group for whom mirdametinib is clinically relevant. However, we would emphasise two clarifications to ensure the definition accurately reflects real-world NF1 practice: Diagnosis of plexiform neurofibroma must be based on clinical and radiological assessment (typically MRI), as PN may be cutaneous, subcutaneous, intramuscular or deep plexus lesions. This diagnostic step is essential before assessing symptoms or operability. “Symptomatic” and “inoperable” should be defined through assessment in an NF1 specialist service (HSS), as attribution of symptoms to PN, assessment of functional impact, and determination of surgical feasibility require specialist multidisciplinary expertise. With these clarifications, the population as defined is appropriate and aligns with current National Highly Specialised Service pathways for NF1.	Comment noted. Thank you. Mirdametinib will be evaluated in line with the population defined in its marketing authorisation for neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas. The population included in the scope reflects the population in the key clinical trial, and the population included in the MHRA marketing authorisation. The identification and diagnosis of this population will be considered as part of the evaluation.
	Nerve Tumours UK	Yes We estimate there are 10 children, and 30-40 adults, in the population with symptomatic inoperable plexiform neurofibromas, that would benefit from this treatment.	Comment noted. Thank you. The population defined in the scope does not define the numbers eligible for treatment. No action required.

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	Childhood Tumour Trust	Is the population defined appropriately? Yes.	Comment noted. Thank you.
Subgroups	Company	There are no additional subgroups that should be considered separately.	Comment noted. Thank you.
	British Paediatric Neurology Association	Yes see comments Appendix B. Need to comment on fact that at present there is no paediatric formulation available and most children under 5 will not reliably be able to swallow tablets. This means that some children are being denied a treatment that may help to slow the growth of their PN.	Comment noted. Thank you. The draft scope currently identifies 'Children and young people aged 2 to 17 years with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas' as a relevant subgroup population to be considered. No action required.
	Association of British Neurologists	There are no robust trial-level data to demonstrate differential treatment effects across predefined subgroups. However, from the perspective of an NHS England Highly Specialised Service for Complex NF1, there are several clinically important subgroups in whom mirdametinib may reasonably be expected to have different levels of benefit and cost-effectiveness, and which therefore warrant separate consideration in the evaluation. First, age is an important clinical distinction. Children and young people often have more active tumour growth and a greater risk of progressive	Comment noted. Thank you. The draft scope currently identifies 'Children and young people aged 2 to 17 years with neurofibromatosis type 1 and symptomatic

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		deformity or future disability, so stabilisation or shrinkage of plexiform neurofibromas may avert significant long-term morbidity. Adults also carry a substantial symptomatic burden but typically have slower-growing PN; the pattern of benefit, optimal treatment duration and impact on long-term function may therefore differ. For this reason, children/young people and adults should be evaluated separately. Second, anatomical location is highly relevant. People with plexiform neurofibromas in high-risk sites such as the spinal canal, paraspinal region, head and neck/airway, or pelvis/sacrum are at greater risk of neurological compromise, airway obstruction, or bowel/bladder dysfunction. In these groups, even modest tumour shrinkage or stabilisation may prevent major functional deterioration or the need for highly complex surgery, increasing both clinical benefit and likely cost-effectiveness. These high-risk anatomical groups differ meaningfully from patients with less critical limb or truncal lesions. Third, people may derive treatment benefit for different primary indications, such as severe pain refractory to standard neuropathic agents, functional impairment, or disfigurement with psychosocial impact. The magnitude and nature of improvement, and therefore quality-of-life gain, may vary according to the predominant clinical problem. It would therefore be appropriate to consider these subgroups separately where possible.	inoperable plexiform neurofibromas' and 'adults aged 18 years and over with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas' as relevant subgroups to be considered. The following subgroup has been added to the scope: People with neurofibromatosis type 1 according to site of symptomatic inoperable plexiform neurofibromas Other subgroups may be considered by the committee if relevant and evidence allows.
	Nerve Tumours UK	Potentially, this will be more clinically effective in children as tumours grow faster in that age group.	Comment noted. Thank you. The draft scope currently identifies 'Children and

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		It is uncertain as to whether the treatment would be more effective depending on the location of the neurofibroma in the body, and further research would be required.	young people aged 2 to 17 years with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas' as a relevant subgroup population to be considered. The following subgroup has been added to the scope: People with neurofibromatosis type 1 according to site of symptomatic inoperable plexiform neurofibromas Other subgroups may be considered by the committee if relevant and evidence allows.
	Childhood Tumour Trust	Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is	Comment noted. Thank you.

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		expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate? No.	
Comparators	Company	For children 3-17 years old, we agree that selumetinib is considered a standard treatment currently used in the NHS. Established clinical management without mirdametinib is not considered standard treatment for children 3-17 years old, and should be removed from the scope. This is based on market research conducted in Q4 2024 with treating physicians from the two NF centres in the UK, as well as from non-NF centres. In adults 18 years old and older, we agree that established clinical management without mirdametinib (i.e., best supportive care) is standard treatment and the appropriate comparator.	Comment noted. Thank you. Established clinical management without mirdametinib has not been removed from the comparators for children. This is because it is intended to capture other treatment options which children may have. The committee will consider which of the comparators included in the scope are relevant.
	British Paediatric Neurology Association	Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included? Yes.	Comment noted. Thank you.
	Association of British Neurologists	I can only comment on the adult comparators but consider that “Established clinical management without mirdametinib” is appropriate.	Comment noted. Thank you.
	Nerve Tumours UK	Comparators:	Comment noted. Thank you. The additional comparators will be

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		Selumetinib (children aged 3 to 18) Standard pain relief: Simple analgesia Gabapentin / Pregabalin Tricyclics Psychological support	identified using the current description "Established clinical management without mirdametinib". No changes required.
	Childhood Tumour Trust	Selumetinib is the only current comparator offered to child patients with PNs and the commissioning of this is extremely limited, with many patients not knowing of the treatment or having it discussed in non-specialist centres. As the remit outlines, there is no comparator for adult care. However, it is important to note that there are no NICE guidelines for the management of NF1, and up to 16 different local or regional guidelines are used across NHS Trusts. (BMJ Open - Alone on our NF1 Island) This variation means that "established clinical management" may differ slightly between centres, highlighting a lack of consistency in care pathways. "At present, '(2022)' there is no agreed upon PN definition, diagnostic evaluation, surveillance strategy, or clear indications for when to initiate treatment and selection of treatment modality. Neuro-Oncology, Volume 24, Issue 11, November 2022, Pages 1827–1844, https://doi.org/10.1093/neuonc/noac146	Comment noted. Thank you for identifying the variation in current practice.
Outcomes	Company	Outcomes measures are appropriate and are expected to capture the most important health related benefits (and harms) of the technology. Please note that airway function or bladder dysfunction was not captured via specific tests or assessments in the ReNeu trial for mirdametinib.	Comment noted. Thank you. The committee will consider which outcomes are relevant.

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	British Paediatric Neurology Association	Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology? Yes.	Comment noted. Thank you.
	Association of British Neurologists	Complete and partial response rate Complete radiological response is almost never seen in plexiform neurofibromas. Partial response is clinically meaningful only when there is an established trajectory of tumour growth, particularly in high-risk anatomical regions (e.g., spinal canal, head and neck, pelvis) where continued enlargement may lead to morbidity. Routine volumetric assessment is often not feasible in standard NHS radiology departments due to the need for specialist software and expertise. Cross-sectional measurements are more practical but less reliable in complex PN. MRI and clinical photography (as used in the paediatric selumetinib pathway) are appropriate adjuncts for documenting change. Growth rate of PN Assessment of growth is most useful where a clear trajectory of growth has been established on serial clinical or imaging assessment. Volumetry can be useful but no universally available due to service constraints, and simpler measures may need to be used in routine practice. Stabilisation of growth can be as important as shrinkage, particularly in high-risk locations. Disfigurement	Comment noted. Thank you. Complete and partial response rate were outcomes included in the key clinical trial and so are included. The committee will consider which outcomes are relevant for decision making.

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		Visible PN may cause contour change or bulk that affects appearance. Clinical photography (as used in paediatric pathways) is helpful for documenting change over time. However, disfigurement is inherently subjective and often difficult to quantify objectively. The impact is therefore better captured through quality-of-life measures, such as InfiQoL (for adults) or other PROMs, which reflect the psychological and social effects of visible PN. Physical functioning Functional outcomes remain central to meaningful benefit. Measures already used in paediatric selumetinib pathways such as: Timed walk tests (e.g., 6-minute walk), and MRC limb power grading are appropriate for adults and children. Changes in mobility, strength, dexterity and limb function should be captured. Visual function Where PN affect the orbital/periorbital region or cranial nerve pathways, formal ophthalmology assessment is essential. This is already a standard component of paediatric MEKi monitoring and appropriate for adults. Airway functioning For head and neck PN, airway assessment may include clinical airway review and sleep studies (as used in paediatric pathways) where obstructive symptoms or sleep-disordered breathing are suspected.	

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		Bowel and bladder continence Relevant for pelvic, sacral and paraspinal PN. Improvements or stabilisation of continence represent significant clinical benefit due to their high impact on daily functioning and independence. Pain Pain is one of the most important symptomatic outcomes, particularly where refractory to neuropathic analgesia. The Numerical Rating Scale (NRS) is practical and widely used. Reduction in pain frequently correlates with improvements in activity, sleep and overall wellbeing. Adverse effects of treatment Long-term therapy requires careful monitoring of safety and tolerability. Existing paediatric MEKi frameworks (e.g., ophthalmology, cardiac, growth and toxicity monitoring) provide a model for adult pathways but will require adaptation and commissioning for adult oncology services Health-related quality of life Quality of life is central to patient benefit. Validated PROMs should be used, such as: PedsQL for children InfiQoL (or equivalent validated adult NF1 tools) for adults. These capture the combined impact of pain, function, appearance, and psychosocial burden.	

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	Nerve Tumours UK	Complete and Partial Response Rate: This is less relevant in a clinical setting as very small changes in volume of the neurofibroma may lead to significant improvement in pain or functional movement. Pain management should be under regional Pain Clinics.	Comments noted. Thank you. Complete and partial response rate were outcomes included in the key clinical trial and so are included. The committee will consider which outcomes are relevant for decision making.
	Childhood Tumour Trust	Long term tolerability, Sleep quality and fatigue, Emotional, psychological and mental wellbeing, Social functioning and participation*. Consideration also to be given around the severity of potential side effects vs those of comparators, which have proven too severe in some patients. (*unless these are included in health related QoL?).	Comment noted. Thank you. These will be captured in the following outcomes: adverse effects of treatment and health-related quality of life.
Equality	Company	No evidence.	Comment noted. Thank you.
	British Paediatric Neurology Association	Would need buy in from all Paediatric Oncology Centres in the UK hence recommendation to include the CCLG in the consultation process. Some patients are experiencing delays in accessing Selumetinib because of oncology centres lacking capacity (NHSE are aware of these issues).	Comment noted. Thank you. The equality issue raised will be included in

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			the equality impact assessment. The committee will consider any relevant equality issues when it makes its recommendations.
	Association of British Neurologists	A significant proportion of people with NF1 have learning disabilities, autism-spectrum traits, or cognitive impairment, and may have difficulties navigating complex referral pathways, scheduling investigations, or articulating symptoms such as pain or functional impairment. These individuals may therefore be disproportionately disadvantaged if access to mirdametinib requires multiple steps across different services, or if the eligibility pathway is not clearly defined and well supported. Furthermore, a high proportion of adults with NF1 experience visible disfigurement, chronic pain, and functional impairment. Any pathway that requires multiple face-to-face assessments, repeated imaging, or complex coordination across services may have a greater adverse impact on people with mobility limitations, visual impairment, airway problems, or bowel/bladder difficulties resulting from their PN. Finally, children currently have access to selumetinib, whereas adults have no systemic treatment option for symptomatic inoperable plexiform neurofibromas. This creates an existing age-related inequity within the NF1 population. The evaluation of mirdametinib provides an opportunity to reduce rather than widen this inequity; therefore, recommendations should	Comment noted. Thank you. The equality issues raised will be included in the equality impact assessment. The committee will consider any relevant equality issues when it makes its recommendations.

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		avoid inadvertently perpetuating an age-based treatment gap unless clinically justified.	
	Nerve Tumours UK	As children from the age of 3 years have access to selumetinib and can continue post transition through to adulthood if it is effective, then it is important for adults to have access to a MEK Inhibitor, for equality purposes. It is important for lay organisations and the Nerve Tumours UK Nurse Advisors to make every effort to act as patient advocates for treatments. NICE should link to the National Centres for NF1 in London (Guys & St Thomas' Hospital) and Manchester (St. Mary's Hospital) to confirm the current transition pathway for selumetinib from childhood to adulthood. The Patient Organisations should dovetail with the specialist NF1 centres to determine how to educate, to inform and support patients particularly those with cognitive impairments.	Comment noted. Thank you. The equality issues raised will be included in the equality impact assessment. The committee will consider any relevant equality issues when it makes its recommendations.
	Childhood Tumour Trust	I feel that people from ethnic minority backgrounds are not adequately represented within the NF1 community or within the available data. Looking at the membership of our charity, it could easily appear that NF1 is a "white condition," which we know is not the case. This lack of representation may mean that people from diverse backgrounds are underdiagnosed or do not receive equitable access to appropriate care, information, and support. • In addition, families with a background of NF1 often face challenges advocating for themselves and their children. Without a particularly knowledgeable healthcare professional who understands the more	Comment noted. Thank you. The equality issues raised will be included in the equality impact assessment. The committee will consider any relevant equality issues when it

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		serious aspects and complications of NF1, these individuals may never receive the correct monitoring or interventions they need. • How can we be sure that those with a PN who are cared for outside the Highly Speicalised Service (around 5000 – 12,000) will even have the chance to be considered for new treatment? • It would be helpful for the Committee to seek evidence on: • The ethnic distribution of NF1 diagnosis and access to specialist services. • The extent to which language, cultural barriers, or health literacy affect diagnosis and follow-up. • Whether families with generational NF1 are receiving consistent and equitable care compared to newly diagnosed families. • How are those with a PN outside the HSS Complex centres monitored and recorded? • This evidence would help ensure that the remit and scope take into account the needs of all groups, particularly those who may currently be underrepresented or disadvantaged.	makes its recommendations.
Other considerations	Company	No comments.	Comment noted. Thank you.
	British Paediatric Neurology Association	Need to consider cost and burden on paediatric oncology centres in the UK where this treatment will be delivered. Our experience with Selumetinib tells us that some oncology centres in the UK are overwhelmed and feel unable to deliver this treatment for what is effectively not a cancer indication. Hence would need to consider additional funding Also need to have a robust transition protocol (currently in process).	Comment noted. Thank you.

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	Association of British Neurologists	Important to consider additional costs associated with delivering this as a treatment especially in adults (as already established pathway in paeds). Would potentially require additional funding for adult CNS clinical supervision of MEK pathway and patients in HSS service, additional therapist and AHP time depending on the clinical outcomes being monitored, funding for additional imaging e.g. volumetry if felt to be clinically necessary for surveillance, support for the HSS services by NHSE to help coordinate referrals and SCA with individual oncology units. Where pain is a main criterion for management, it will need to be mandated that all other standard options for pain management have been explored.	Comment noted. Thank you. All costs associated with introducing the technology will be taken into account.
	Nerve Tumours UK	The decision on whether to use Mirdametinib to treat children and adults with symptomatic inoperable plexiform neurofibromas, would be made at the National Centres for NF in London (Guys & St. Thomas Hospital) & Manchester (St. Mary's Hospital). However the drug would be prescribed by local paediatric and adult oncology units, who are already under pressure and so appropriate consideration regarding funding should be given to these units and to the National NF1 Centres, to deal with these complex issues.	Comment noted. Thank you.
	Childhood Tumour Trust	No comments.	Comment noted. Thank you.
Questions for consultation	Company	Questions for consultation 1. How is symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis defined?	Thank you for providing these responses.

Section	Consultee/ Commentator	Comments [sic]	Action
		Response: Mutations in the NF1 gene result in loss of production or reduced function of neurofibromin, causing the wide spectrum of clinical findings (Shen et al. 1996). NF1 is characterised by diverse, progressive, cutaneous, neurological, skeletal and neoplastic manifestations with no standard drug treatment options available. The manifestation of the NF1 clinical diagnostic criteria typically appears with café-au-lait macules, axillary and/or inguinal freckling and finally neurofibromas (DeBella et al. 2000). Patients with NF1 develop both non-malignant and malignant tumours at increased frequency throughout life (Gutmann et al. 2017, Seminog and Goldacre 2013). Neurofibromas are the most common type of tumor that develop in patients with NF1. Neurofibromas are non-malignant peripheral nerve sheath tumours that are comprised of a mixture of Schwann cells, fibroblasts, perineurial cells, macrophages, endothelial cells, pericytes (Hirbe et al. 2014), and mast cells (Tucker et al. 2011). The Schwann cells may be abnormal in NF1 patients, having angiogenic and invasive properties in a specific tumour (Sheela et al. 1990) and are therefore the primary tumour cells of the neurofibroma (Carroll and Ratner 2008, Maertens et al. 2006). Neurofibromas are commonly found in the skin but may be found along peripheral nerves or deeper inside the body, and along nerve roots adjacent to the spine. When a neurofibroma extends longitudinally along a nerve and involves multiple fascicles, it is classified as a plexiform neurofibroma (PN). PNs may be located superficially and associated with overgrowth of skin and soft tissues, may be located deep inside the body, or may have both superficial and deep components. Deeper PNs tend to appear as thickened nerves and can grow into a complex mass consisting of a network of enlarged nerves. The lesions are usually congenital and tend to grow most rapidly during childhood (Dombi et al. 2007). Whole body imaging reveals PNs in 30% to 50% of patients with NF1 (Plotkin et al. 2012). PNs rarely regress spontaneously, and in many patients their growth is relentless. PNs represent a major cause of morbidity and disfigurement in individuals with NF1,and when symptomatic, are	

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		associated with increased mortality (Prada et al. 2012, Rasmussen et al. 2001). As tumour growth progresses, such lesions produce dysfunction, pain, and cosmetic disfigurement and can compress the airway or spinal cord. As examples, PNs may infiltrate the orbit and displace the globe and compromise vision; paraspinal tumours can compress the spinal cord and cause paralysis; tumours in mediastinum may compress the trachea or great vessels; and tumours of the extremities can cause local nerve infiltration, progressive neurologic deficit and often unremitting pain (Needle et al. 1997). 2. Can you provide an estimate of how many people with symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis would expect to be treated with mirdametinib in England? Response: We estimate that [redacted] with symptomatic, inoperable NF1-PN will be treated with mirdametinib in England. 3. Which treatments are considered to be established clinical practice in the NHS for symptomatic inoperable plexiform neurofibromas? Response: Treatments considered to be established clinical practice in the NHS for symptomatic inoperable plexiform neurofibromas include selumetinib for the paediatric population, and best supportive care for the remaining population with symptomatic inoperable plexiform neurofibromas. 4. How do treatment options and managing the condition differ for children (aged 2 to 17 years) and adults (aged 18 years and over)? Response: The currently available treatment options for neurofibromatosis type 1 with symptomatic inoperable plexiform neurofibromas (PNs) include	

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		selumetinib which is licensed for the treatment of symptomatic, inoperable PNs in pediatric patients with NF1, aged 3 years and above. This means that for children younger than 3 and adults 18+ years old, there is no licensed treatment option in the UK. Another group of patients for whom treatment options and management may differ are those who struggle with swallowing capsules, such as children younger than 7 and adults with head and neck PNs. Selumetinib is currently available in a capsule formulation, which may not be feasible for these patients to use. 5. Would children and adults be managed by the same treatment centres? Response: Yes, as there are only 2 nationally commissioned Complex NF1 Service Centers in the UK that provide care for NF1 patients, especially for patients with complicated plexiform neurofibromas: • Central Manchester University Hospitals NHS Foundation Trust • Guys and St. Thomas' NHS Foundation Trust 6. Is selumetinib considered standard of care for people aged 3 to 17 years? Response: Yes, this is based on market research conducted in Q4 2024 with treating physicians from the two NF centres in the UK, as well as from non-NF centres. 7. How would mirdametinib fit into the clinical pathway for symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis? Response: Mirdametinib would be used as a 1st line treatment for symptomatic inoperable plexiform neurofibromas associated with NF1 and	

Section	Consultee/ Commentator	Comments [sic]	Action
		no differences would be expected to the clinical pathway that is currently established for selumetinib in paediatric patients. 8. Please select from the following, will mirdametinib be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): Response: D: Specialist centres will receive referrals for patients who are eligible for and would benefit from mirdametinib. These patients get referred to a tertiary oncology center where mirdametinib will be prescribed. 9. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Response: The setting for prescribing and routine follow-up do not differ between the intervention and comparators. For patients who are currently treated by NF1 specialists there should not be a change in the setting for prescribing and routine follow-up. However, especially in the adult population, a significant number of patients are not under the care of NF1 specialists is seen in the market research conducted in Q4 2024 with treating physicians from the two NF centres in the UK as well as from non-NF centres. 10. Are the outcomes listed appropriate? Response: Outcomes listed are appropriate.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Please note that airway function or bladder dysfunction was not captured via specific tests or assessments in the ReNeu trial for mirdametinib. 11. Are there any subgroups of people in whom mirdametinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Response: There is no evidence for any subgroups where miredametinib is expected to be more clinically or cost effective. Paediatric and adult populations would be examined separately in this appraisal due to the different comparators relevant for each group. 12. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which mirdametinib is licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Response: No comments.	

Section	Consultee/ Commentator	Comments [sic]	Action
		13. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. Response: No evidence. 14. NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation). • Will the intervention be used to treat the same population as the comparator(s)? Response: Yes – for the paediatric population mirdametinib would be used to treat the same population as for selumetinib. For the adult population mirdametinib would be used to treat the same population who are currently treated with best supportive care. • Overall is the technology likely to offer similar or improved health benefits compared with the comparators? Response: Mirdametinib is likely to provide similar or greater health benefits than selumetinib in children. Mirdametinib is likely to provide greater health benefits than best supportive care in adults.	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Would it be appropriate to use the cost-comparison methodology for this topic? Response: The company believes that a cost-comparison methodology is appropriate for the paediatric population, where the most appropriate comparator is selumetinib (standard of care). Mirdametinib is likely to provide equal or greater clinical benefits compared to selumetinib. Provided that the overall costs are expected to be broadly similar, this aligns with NICE's criteria for cost comparison, which require evidence of similar or greater clinical effectiveness at a similar or lower cost compared with a technology recommended by NICE for the same indication.	
	British Paediatric Neurology Association	Questions for consultation. How is symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis defined? Can you provide an estimate of how many people with symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis would expect to be treated with mirdametinib in England? I can only comment on paediatric population and estimate 10 per year Which treatments are considered to be established clinical practice in the NHS for symptomatic inoperable plexiform neurofibromas? Conservative treatment (includes pain management, physiotherapy, psychology), surgery (debulking or excision) and MEK inhibitors (Trametinib	Thank you for providing these responses.

		as part of clinical trial initially and now roll over study) and Selumetinib initially as part of clinical trial and now on NHS How do treatment options and managing the condition differ for children (aged 2 to 17 years) and adults (aged 18 years and over)? At present there is no medical treatment available for adults with NF1 symptomatic PN as Selumetinib is only licensed for children age 3- 18 years; unless they started treatment as a child and did not have a break from it. Would children and adults be managed by the same treatment centres? They would be assessed for eligibility in the National Complex NF1 service (if stick to same treatment pathway as for Selumetinib) but No children would receive treatment in paediatric oncology centres, young adults in TYA centres where available and adults in adult oncology centres Is selumetinib considered standard of care for people aged 3 to 17 years? Yes How would mirdametinib fit into the clinical pathway for symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis? In the paediatric setting, it would be used for children who cannot swallow tablets reliably. Could also be tried in children who have not responded to or have not tolerated Selumetinib or Trametinib Please select from the following, will mirdametinib be: A. Prescribed in primary care with routine follow-up in primary care No B. Prescribed in secondary care with routine follow-up in primary care No C. Prescribed in secondary care with routine follow-up in secondary care No D. Other (please give details): As per current pathway for Selumetinib, we propose that all potentially eligible children should be evaluated in the NHSE National NF service and eligibility then discussed in the National MEK inhibitor MDT. This is to ensure children get appropriate treatment and don't	

		miss out on other potential treatments eg debulking surgery. Once eligibility confirmed then we would refer to the child's regional oncology centre to deliver the treatment and the clinical monitoring of the PN would be performed at the National NF centre For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Pathway would be same as for Selumetinib as defined in the NHSE Selumetinib Shared Care Agreement Are the outcomes listed appropriate? Yes Are there any subgroups of people in whom mirdametinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Only by virtue of the fact that it has a paediatric formulation so younger children would be able to access it NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which mirdametinib is licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities.	

Section	Consultee/ Commentator	Comments [sic]	Action
		• No to all of these but issue may arise with certain oncology centres refusing to treat children as they do not have capacity due to lack of extra finding as we have experienced with Selumetinib Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. Listing CCLG as a stakeholder and asking them to collect views from UK paediatric oncology centres and for young people and adults TYA and adult oncology centres NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation). • Will the intervention be used to treat the same population as the comparator(s)? It would target a different group of patients as mentioned • Overall is the technology likely to offer similar or improved health benefits compared with the comparators? • Would it be appropriate to use the cost-comparison methodology for this topic? Important to consider that at present as there is no other paediatric formulation of a MEK inhibitor available there will be limited data on comparison of different MEK inhibitors in this age group. Additionally, there is no current MEK inhibitor available for adults (unless they started as a child)	
	Association of British Neurologists	Questions for consultation (additional questions from Appendix B) How is symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis defined? A diagnosis of plexiform neurofibroma must be established based on combined clinical and specialist radiological assessment (typically MRI).	Thank you for providing these responses.

Section	Consultee/ Commentator	Comments [sic]	Action
		PN is considered symptomatic when it causes one or more of the following, confirmed through assessment in an NF1 specialist service: • Pain o Persistent PN-related pain o Not responsive to standard pain-management approaches, including adequate trials of neuropathic analgesia o Pain significantly impairing sleep, mobility, education, work or daily activities o It is expected that patients with PN related pain would have had assessment from local pain management services • Functional impairment o Weakness, gait disturbance, limb dysfunction, or fine motor impairment o Sensory disturbance or neuropathic symptoms (e.g., radiculopathy) o PN-related impairment of swallowing, vision, airway function, bladder or bowel impairment o Threat to function; typically from current or impending compression of the airway, spinal cord, major vessels o Skeletal distortion or progressive structural change caused by PN	

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		• Disfigurement with psychosocial morbidity ○ Visible PN causing significant distress, social withdrawal, limitations in education/employment or measurable psychological burden • Progressively enlarging lesions (clinically defined) ○ A fixed volumetric threshold (e.g., 20%) is not used in adult NF1 practice. ○ Growth is clinically significant when: ▪ Enlargement is accompanied by progressive symptoms or functional decline, or ▪ The PN lies in a high-risk anatomical region (spinal canal, brachial plexus, pelvis, head & neck), or ▪ Specialist NF1 radiology confirms a reliable growth trajectory posing medium-term risk to neurological or anatomical function. Definition of “inoperable” PN • A PN is deemed inoperable following review by a surgeon experienced in NF1-related tumour surgery when: ○ Surgical complexity or risk ○ Complete resection cannot be achieved without unacceptable neurological or functional morbidity, or	

Section	Consultee/ Commentator	Comments [sic]	Action
		○ The PN is intertwined with major nerves or vascular structures ○ The tumour is diffuse, infiltrative, or involves multiple fascicles or plexus regions such that meaningful resection cannot be achieved ○ Resection would result in greater loss of function than anticipated clinical benefit Can you provide an estimate of how many people with symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis would expect to be treated with mirdametinib in England? As one of the NHS England Highly Specialised Services (HSS) for Complex NF1, we maintain detailed cohort data for adults with NF1. To date, we have assessed ~3000 adults with NF1 within our service at Guy's & St Thomas' Hospital. Of this cohort ~17% have had a symptomatic plexiform neurofibroma (PN) at some point. It is important to note that this 17% figure reflects a specialist tertiary HSS cohort and therefore: • Represents patients who have been referred because of complexity, • Is not representative of the prevalence of symptomatic PN in the general NF1 population, and • Almost certainly overestimates the true proportion of adults with symptomatic PN in the wider NHS population. Even within our geographical catchment, not all adults with symptomatic PN are referred to us, and referral patterns differ between regions and services.	

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		The true symptomatic-PN prevalence in the adult NF1 population is therefore expected to be lower than the 17% observed in our tertiary cohort. Within our current GSTT cohort, we estimate that approximately 50–100 adults have symptomatic, inoperable PN with clinically significant unmet need who would likely benefit from a MEK inhibitor (including mirdametinib), either now or in the foreseeable future. We do not hold national data outside the two HSS centres. However, if we cautiously assume that the Manchester HSS has a similar adult NF1 caseload and similar referral complexity, we estimate: ~100–200 adults under HSS follow-up nationally may meet criteria for mirdametinib, with A broader realistic range of ~100–300 adults in England when accounting for patients not yet known to either HSS centre. This estimate is deliberately conservative, based solely on real-world HSS data and acknowledging the limitations of current national NF1 surveillance. More precise modelling would require structured epidemiological data and a national adult NF1 PN registry, which do not presently exist. Which treatments are considered to be established clinical practice in the NHS for symptomatic inoperable plexiform neurofibromas? In our Highly Specialised Service (HSS) for Complex NF1 at Guy's & St Thomas', established clinical practice for adults with symptomatic inoperable plexiform neurofibromas consists of: 1. Specialist NF1 multidisciplinary assessment a. All patients with suspected symptomatic PN are reviewed in an NF1 specialist MDT, with: b. Clinical assessment (attribution of symptoms to the PN) c. Dedicated MRI (and other imaging as required)	

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		d. Referral to/review by by NF-experienced peripheral nerve / neurosurgical / ENT / orthopaedic surgeons to determine appropriateness and feasibility of surgery. e. Education around malignant peripheral nerve sheath tumour risk 2. Non-surgical / supportive management a. For adults under our care with symptomatic inoperable PN, established management includes: b. Pain management and referral to specialist pain services where needed. c. Physiotherapy and occupational therapy to maintain mobility, strength and function d. Targeted input from other specialties according to PN site and complications (e.g. spinal, orthopaedic, neurosurgical, ENT, sleep/respiratory, urology, colorectal). e. Psychological support via NF-specific clinical psychology, where pain, disfigurement or functional disability are impacting mental health, relationships or employment. f. Monitoring for progression of symptoms and function, and surveillance for possible malignant transformation. How do treatment options and managing the condition differ for children (aged 2 to 17 years) and adults (aged 18 years and over)?	

Section	Consultee/ Commentator	Comments [sic]	Action
		Within the nationally commissioned Highly Specialised Services (HSS) for Complex NF1, the core principles of assessment and management of plexiform neurofibromas (PN) are essentially the same for children and adults. In children there is more likely to be age-related growth in plexiform and therefore children require closer monitoring. Adults generally have slower or stable PN growth, so monitoring is usually annual or symptom-driven. At present selumetinib is available for children (<18yrs) with symptomatic plexiform and there are no currently available MEK ihibitors for use in adults. Would children and adults be managed by the same treatment centres? Both NHS England–commissioned Highly Specialised Services (HSS) for Complex NF1 (Guy's & St Thomas' and Manchester) provide national expertise for both paediatric and adult patients. For paediatrics, MEK inhibitors (currently selumetinib) are available only for children under NICE HST20. Delivery occurs through tertiary paediatric oncology units, with established pathways and national shared-care arrangements. This is not a new pathway; the introduction of new paediatric MEKi (e.g., mirdametinib) would sit within an existing paediatric oncology infrastructure. For adults, there is currently no routinely commissioned systemic therapy for adults with NF1 PN, and therefore no established adult MEK inhibitor pathway within the NHS. If mirdametinib is approved for adults, treatment delivery would need to occur through adult medical oncology services (secondary or tertiary), but the operational pathway is not currently in place. Is selumetinib considered standard of care for people aged 3 to 17 years? It is an available treatment option for some children with symptomatic inoperable plexiform however there are significant monitoring requirements, potential side effects and commitment to treatment requirements. Not all patients have sufficiently significant symptoms to warrant MEK inhibitor therapy but all those who are felt by the paediatric complex NF team to be	

Section	Consultee/ Commentator	Comments [sic]	Action
		eligible would be expected to be discussed in the joint national MEKi MDT (with Manchester). The 'standard of care' is more complex and encompasses the MDT approach to managements – selumetinib is one of the options for treatment. How would mirdametinib fit into the clinical pathway for symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis? For adults, any patients under the HSS complex service would be assessed in clinic, and where appropriate discussed in a joint MDT with Manchester to determine eligibility for MEK inhibitor therapy. IF approved, they would be referred to their local oncology service delivering this treatment which would be supported by a shared care agreement (as for paeds and transition). These have yet to be developed. Clinical responsibility (as per the current selumetinib shared care agreement) for prescribing and monitoring drug related issues would,lie with oncology and overall support and management of their NF1 would be with the adult complex NF1 service. Please select from the following, will mirdametinib be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): D – The determination for eligibility would be with the HSS NF1 service but delivery of the drug, prescription and monitoring would be with either secondary or tertiary oncology services locally.	

Section	Consultee/ Commentator	Comments [sic]	Action
	Nerve Tumours UK	The intervention will not be used to treat the same population as the comparators. It will be used to treat children under 3 years of age, those unable to swallow tablets, and adults. The technology is likely to offer similar or improved health benefits compared to the comparators. It would be appropriate to use the cost-comparison methodology to appraise this topic.	Thank you for providing these responses.
	Childhood Tumour Trust	• How is symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis defined? **Already outlined and appropriately defined** • Can you provide an estimate of how many people with symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis would expect to be treated with mirdametinib in England? **Based on the data of approximately 20,000 diagnosed, 30% - 50% with PN, halved to cover data around inoperable PN around 3000 – 5000. However although they may be inoperable they may not be symptomatic but data only gives inoperable**. • Which treatments are considered to be established clinical practice in the NHS for symptomatic inoperable plexiform neurofibromas? **In children, selumetinib, in adult, pain management or chemotherapy for an MPNST but there are no clear establish guidelines** • How do treatment options and managing the condition differ for children (aged 2 to 17 years) and adults (aged 18 years and over)? **Only one drug is available and that is for child care. There is nothing for adults. Children are usually seen by a paediatrician and**	Thank you for providing these responses.

Section	Consultee/ Commentator	Comments [sic]	Action
		multidisciplinary care is common. In adults unless they are under a Complex centre they rely on primary care. • Would children and adults be managed by the same treatment centres? **Potentially not, as existing centres exist and operate well for child care at specialist paediatric oncology units across England.** • Is selumetinib considered standard of care for people aged 3 to 17 years**? It is for those who receive it, but this is incredibly limited** • How would mirdametinib fit into the clinical pathway for symptomatic inoperable plexiform neurofibromas associated with type 1 neurofibromatosis? **It would offer an alternative medical option for adults and children, which could provide wider accessibility** • Please select from the following, will mirdametinib be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): **This is unclear, but we would expect this to be via secondary care for both prescribing and follow up.** For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. • • Are the outcomes listed appropriate? **Yes** • Are there any subgroups of people in whom mirdametinib is expected to be more clinically effective and cost effective or other groups that should	

Section	Consultee/ Commentator	Comments [sic]	Action
		be examined separately? **None. There is no comparator in adult care so it would apply to all**. • NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which mirdametinib is licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; **Please see above re: low representation from ethnic minority communities in the NF community, therefore there is likelihood of bias or limited knowledge from these groups.** • could have any adverse impact on people with a particular disability or disabilities. **This is unlikely and may actually be a positive step for adults with disabilities as it provides a pathway that may minimise the potential for surgical intervention**. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. **Patient independent advisory groups will help to gather this viewpoint**	
Additional comments on the draft scope	Nerve Tumours UK	Any additional comments on the draft scope: Consideration should be given to pregnancy and conception.	Comment noted. Thank you. NICE can only make recommendations within the marketing

Section	Consultee/ Commentator	Comments [sic]	Action
			authorisation. The summary of product characteristics will outline any concerns related to pregnancy and conception which should be followed when using any recommendations. As pregnancy is a protected characteristic, this will be included in the equality impact assessment.

References:

Carroll SL, Ratner N (2008) How does the Schwann cell lineage form tumors in NF1? Glia 56 (14): 1590-1605

DeBella K, Szudek J, Friedman JM (2000) Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 105 (3 Pt 1): 608-614

Dombi E, Solomon J, Gillespie AJ et al. (2007) NF1 plexiform neurofibroma growth rate by volumetric MRI: relationship to age and body weight. Neurology 68 (9): 643-647

Ejerskov C, Farholt S, Nielsen FSK et al. (2023) Clinical Characteristics and Management of Children and Adults with Neurofibromatosis Type 1 and Plexiform Neurofibromas in Denmark: A Nationwide Study. Oncol Ther 11 (1): 97-110

Gutmann DH, Ferner RE, Listernick RH et al. (2017) Neurofibromatosis type 1. Nature Reviews Disease Primers 3 (1): 17004

Hirbe AC, Pekmezci M, Dahiya S et al. (2014) BRAFV600E mutation in sporadic and neurofibromatosis type 1-related malignant peripheral nerve sheath tumors. Neuro Oncol 16 (3): 466-467

Jensen SE, Patel ZS, Listernick R et al. (2019) Lifespan Development: Symptoms Experienced by Individuals with Neurofibromatosis Type 1 Associated Plexiform Neurofibromas from Childhood into Adulthood. J Clin Psychol Med Settings 26 (3): 259-270

Maertens O, Brems H, Vandesompele J et al. (2006) Comprehensive NF1 screening on cultured Schwann cells from neurofibromas. Hum Mutat 27 (10): 1030-1040

Moertel CL, Hirbe AC, Shuhaiber HH et al. (2025) ReNeu: A Pivotal, Phase IIb Trial of Mirdametinib in Adults and Children With Symptomatic Neurofibromatosis Type 1-Associated Plexiform Neurofibroma. Journal of Clinical Oncology 43 (6): 716-729
Mol I, Bell T, Hu Y et al. (2025) Indirect Treatment Comparison (ITC) of Mirdametinib and Selumetinib for the Treatment of Children with Neurofibromatosis Type 1-Associated Plexiform Neurofibromas (NF1-PN). Value in Health 28 (6): S45
Needle MN, Cnaan A, Dattilo J et al. (1997) Prognostic signs in the surgical management of plexiform neurofibroma: the Children's Hospital of Philadelphia experience, 1974-1994. J Pediatr 131 (5): 678-682
Plotkin SR, Bredella MA, Cai W et al. (2012) Quantitative assessment of whole-body tumor burden in adult patients with neurofibromatosis. PLoS One 7 (4): e35711
Prada CE, Rangwala FA, Martin LJ et al. (2012) Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr 160 (3): 461-467
Rasmussen SA, Yang Q, Friedman JM (2001) Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet 68 (5): 1110-1118
Saleh M, Dib A, Beaini S et al. (2023) Neurofibromatosis type 1 system-based manifestations and treatments: a review. Neurological Sciences 44 (6): 1931-1947
Seminog OO, Goldacre MJ (2013) Risk of benign tumours of nervous system, and of malignant neoplasms, in people with neurofibromatosis: population-based record-linkage study. Br J Cancer 108 (1): 193-198
Sheela S, Riccardi VM, Ratner N (1990) Angiogenic and invasive properties of neurofibroma Schwann cells. J Cell Biol 111 (2): 645-653
Shen MH, Harper PS, Upadhyaya M (1996) Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet 33 (1): 2-17
Tucker T, Riccardi VM, Sutcliffe M et al. (2011) Different patterns of mast cells distinguish diffuse from encapsulated neurofibromas in patients with neurofibromatosis 1. J Histochem Cytochem 59 (6): 584-590

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Crohn’s and Colitis UK