National Institute for Health and Care Excellence

Health Technology Evaluation

Dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	The Brain Tumour Charity	The Brain Tumour Charity believes that this technology should be assessed under the HST criteria. Following the NICE methods review, there are four criteria for HST and we believe that this fits three of the four criteria: • Incidence is no greater than 1:50,000 population in England, approximately 1 in 100,000. • Gliomas significantly shortens life or severely impair quality of life. • There are no other satisfactory treatment options for gliomas, and the technology is likely to offer significant additional benefit over existing treatment options.	Thank you for your comment. This topic will be routed as a single technology appraisal. Criterion 2 for eligibility for HST **'**Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications' was not met. Therefore, it is not appropriate for this topic to be routed as an HST.

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	Children's Cancer and Leukaemia Group (CCLG)	This is appropriate and correct route of STA.	Thank you for your comment. This topic will be routed as a single technology appraisal. Criterion 2 for eligibility for HST **'**Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications' was not met. Therefore, it is not appropriate for this topic to be routed as an HST.
	Novartis Pharmaceuticals	Novartis wishes NICE to reconsider their assessment for HST criteria. • HST criteria 2: As the liquid formulation of dabrafenib with trametinib will be licenced as a new product, marketed under a new brand name and there will be no subsequent licenced indications for this formulation, Novartis believes this criteria to be met. • HST criteria 4: There are no NICE recommended treatments for glioma in children and young adults. Furthermore, evidence from the clinical trial demonstrates a significant benefit in progression-free survival and response rates compared with chemotherapy in patients with low grade glioma. Efficacy data in high-grade glioma demonstrate a substantial improvement in terms of response rate,	Thank you for your comment. This topic will be routed as a single technology appraisal. Criterion 2 for eligibility for HST **'**Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications' was not met. Therefore, it is not appropriate for this topic to be routed as an HST.

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		progression-free survival and overall survival compared with historical cohorts.	
Wording	The Brain Tumour Charity	No further comments on the wording.	Thank you.
	Children's Cancer and Leukaemia Group (CCLG)	Yes the wording is appropriate BUT there will be rare cases of BRAFV600E mutated gliomas occurring in under 1 old patients that will be excluded by this and of course patients >18 years also excluded.	Thank you for your comment. The population included in the remit reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The committee can only make recommendations within the marketing authorisation. No changes needed.
	The Royal College of Pathologists	The wording is adequate for the remit of the issue.	Thank you for your comment.
	Novartis Pharmaceuticals	Novartis considers the wording of the remit to be appropriate.	Thank you for your comment.
	The Brain Tumour Charity	The Brain Tumour Charity would request that this process be considered a priority for assessment. The impact of this disease on both the patients and	Thank you for your comment. This evaluation

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Additional comments on the draft remit		their families is considerable and well documented in our report *Losing my place: the reality of childhood with a brain tumour* It is particularly pertinent, given that this treatment is aimed at a population during their formative years, when the impact of the disease and treatment will have a considerable ongoing effect on the person including ability to work, social interactions and education. The majority of patients in the described cohort will also be very dependent on their parents or carers in order to look after them. And we know that of the parents of those diagnosed with a brain tumour, nearly three quarters report that their own mental health was affected. More broadly 95% of parents reported that a diagnosis had affected the lives of a sibling, showing the considerable familial impact beyond that of the patient. As such, we request that this be considered with some urgency and be prioritised ahead of medicines where there are already have well established and impactful treatments.	has been scheduled into the work programme.
	Children's Cancer and Leukaemia Group (CCLG)	I do note that the FDA have approved these agents in 2 paediatric indications: *BRAF V600E Mutation-Positive Low-Grade Glioma dabrafenib is indicated, in combination with trametinib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy 16 March 2023*	Thank you for your comment. The population included in the remit reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The committee will be able to

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		And *Accelerated approval to dabrafenib in combination with trametinib for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. June 22, 2022.* There are other paediatric BRAFV600E indication such as Langerhans Cell Histiocytosis (LCH) and rarer other solid tumours that the FDA has reviewed and approved as above. Will these be considered separately?	make recommendations within the population specified within the marketing authorisation. NICE will evaluate all licence extensions if a referral is made. No changes needed.
	The Royal College of Pathologists	It is commendable that this health technology evaluation considers the introduction of BRAF pathway inhibitors in young people (children and young adults until age of 17) with a BRAF mutant intrinsic tumour. However, they should be a justification why this eligibility should end at age of 17, and why it is not extended to older age groups, either TYA (up to 25 years of age) and potentially also in people until their thirties, in whom such tumours also exist.	Thank you for your comment. The population included in the remit reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The remit has been updated to remove reference to a specific age range, and the remit now refers to children and young people. The committee will be able to make recommendations within the population

Section	Stakeholder	Comments [sic]	Action
			specified within the marketing authorisation.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	The Brain Tumour Charity	The Brain Tumour Charity believes that the background information is incomplete. The impact on young people has been ignored, which helps to speak to the quality of life of these patients – one of the criteria for defining the proposed route. The impact of living with a brain tumour as a child is: • More than eight out of ten (84%) said their brain tumour had made them feel lonely • Seven out of ten (70%) said they had difficulty doing things outside the house • More than a third (36%) of those who had symptoms said they experienced difficulties with thinking, concentrating and processing information • Three out of ten of those with symptoms reported changes to their personality • It additionally fails to take into account the impact of parents/carers following a diagnosis.	Thank you for your comment. The background section of the scope has been updated.

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		The impact on parents/carer can include: • Almost three quarters said their child's brain tumour had had a moderate or severe impact on their own mental health • 90% said they felt lonely or isolated as a result of their child's brain tumour diagnosis For further information on the impact of a childhood brain tumour diagnosis, please read our full survey and report on this issue: https://rb.gy/7vbs9	
	Children's Cancer and Leukaemia Group (CCLG)	The use of radiotherapy/ proton Beam therapy for Paediatric Low-Grade Glioma is complex and not solely defined by age i.e. 10 years but location, size and responsiveness to prior therapies.	Thank you for your comment. The background section of the scope has been updated.
	The Royal College of Pathologists	The information appears reasonably accurate, as described in the background.	Thank you for your comment.
	Novartis Pharmaceuticals	Novartis agree that the background information provided accurately describes the current treatment pathway for patients. With regards to the prevalence of glioma we would like to highlight that BRAF V600E mutation is found in 15-20% cases of paediatric low grade glioma. We would also like to use this opportunity to highlight that the liquid formulation of dabrafenib with trametinib being appraised will have a	Thank you for your comment. There are multiple sources with varying estimates for the prevalence of BRAF V600E mutation in high- and low-grade glioma. The background section of the

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		different brand name to the tablet and therefore won't be named Tafinlar and Mekinist.	scope has been updated to account for the range of published prevalence estimates. The technology section of the scope has been updated to remove reference to Tafinlar and Mekinist.
Population	The Brain Tumour Charity	No further comments.	Thank you.
	Children's Cancer and Leukaemia Group (CCLG)	The population reflects that covered by the clinical trial however as already mentioned there will be rare cases of BRAFV600E mutated gliomas occurring in under 1 old patients and a cohort of patients >18 years who will be excluded.	Thank you for your comment. The population included in the scope reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The population in the scope has been updated to remove reference to a specific age range, and now refers to children and young people. The committee will be able to make

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			recommendations within the population specified within the marketing authorisation.
	The Royal College of Pathologists	Please see above my comments on the draft remit: Why is it limited to up to 17 years of age, and not also considered for teenagers and young adults up to the age of 25, or, in fact to adults. What is the rationale for the age restriction? Is there evidence that BRAF inhibitors are more effective in people in the proposed age group than in older people? Should one not evaluate other eligibility criteria, which could be either pathologically/molecularly defined (malignancy grade, other molecular profiles), or clinically defined, for example based on the performance status, or certain imaging parameter?	Thank you for your comment. The population included in the scope reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The population in the scope has been updated to remove reference to a specific age range, and now refers to children and young people. The committee will be able to make recommendations within the population specified within the marketing authorisation.
	Novartis Pharmaceuticals	Novartis considers the population stated in the draft scope to be appropriate.	Thank you for your comment.
Subgroups	The Brain Tumour Charity	No further comments.	Thank you.

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	Children's Cancer and Leukaemia Group (CCLG)	*Low-grade glioma that requires systemic treatment* This is correct and should be considered for both newly diagnosed and progressive relapsed paediatric BRAFV600E mutated low-grade glioma at any stage. *High-grade glioma that has relapsed, progressed or failed to respond to previous systemic treatment.* There is a strong feeling academically that dabrafenib+trametinib may be a more effective adjuvant treatment than the current standard of care of Temozolomide when added to radiation post-surgery as most of these tumours are MGMT Unmethylated. However, in the trial only patients progressing after with High-grade glioma that has relapsed, progressed or failed to respond to previous systemic treatment were included.	Thank you for your comment. The subgroups included in the scope reflects the subgroups in the key clinical trial, which is expected to inform the marketing authorisation in this indication. This includes the positioning in the treatment pathway for high-grade glioma. The committee can only make recommendations within the marketing authorisation.
	The Royal College of Pathologists	Please see my question above, i.e. I am less concerned about subgroups within the proposed age range, but an extension to older patients as well.	Thank you for your comment. The population included in the scope reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The population in the scope has been updated to remove reference to a specific age range, and now refers to children and young people. The committee will be able to make

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			recommendations within the population specified within the marketing authorisation.
	Novartis Pharmaceuticals	The subgroups considered are relevant.	Thank you for your comment.
Comparators	The Brain Tumour Charity	No further comments.	Thank you for your comment. The comparators have been updated based on feedback at a scoping workshop.
	Children's Cancer and Leukaemia Group (CCLG)	For the proposed subgroups and indications these broad comparators are current standard of care.	Thank you for your comment. The comparators have been updated based on feedback at a scoping workshop.
	The Royal College of Pathologists	In my opinion (as a neuropathologist) the comparators are well described, but the ultimate opinion should be given by medical oncologists.	Thank you for your comment. The comparators have been updated based on feedback at a scoping workshop.
	Novartis Pharmaceuticals	The comparators considered are relevant.	Thank you for your comment. The comparators have been updated based on feedback at a scoping workshop.

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Outcomes	The Brain Tumour Charity	The Brain Tumour Charity believes that the outcomes are largely correct and match the primary and secondary end points in the clinical trials. There is one area that requires amendment and one that requires addition. The health related quality of life must be amended to broader aspects of quality of life, especially considering that this evaluation is considering children. The impact and disruption of a condition like this will have an impact on their schooling, social lives, future employment prospects and personality. This must be included in any consideration related to quality of life. Given the evaluation is aimed at a paediatric population the impact on those who care for them is arguably greater. This is not currently included in the outcomes, but we believe that it should be. The evaluation should consider the psychological, physical and economic impact of those caring for those diagnosed.	Thank you for your comment. The outcomes listed in the scope are not intended to be fully exhaustive. The committee may consider aspects that contribute to health-related quality of life within this broad outcome. Health-related quality of life of carers has been included in the outcomes listed in the scope.
	Children's Cancer and Leukaemia Group (CCLG)	These are appropriate.	Thank you for your comment.
	The Royal College of Pathologists	Outside my core expertise	Thank you.

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	Novartis Pharmaceuticals	Duration of response should be included as an outcome as this is a clinically relevant outcome.	Thank you for your comment. Duration of response has been added as an additional outcome.
Equality	The Brain Tumour Charity	No further comments.	Thank you.
	Children's Cancer and Leukaemia Group (CCLG)	No concerns.	Thank you for your comment.
	The Royal College of Pathologists	In my opinion (which is experience based but not necessarily evidence-based in this particular topic) the inclusion criteria are pathologically/molecular pathology-defined. This should not introduce a bias as such when making a decision for treatment.	Thank you for your comment.
	Novartis Pharmaceuticals	No equality considerations required.	Thank you for your comment.
Other considerations	The Brain Tumour Charity	The Brain Tumour Charity believes that further consideration should be given to providing the treatment upfront, ahead of radiotherapy in order to reduce sequelae.	Thank you for your comment. The committee will consider the positioning of the treatment in the pathway, within the marketing authorisation.

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	Children's Cancer and Leukaemia Group (CCLG)	Value of a paediatric formulation to allow administration in patients either to young to reliably swallow tablets or unable due to neurological disability. Stability to administer of required by nasogastric or gastrostomy tube.	Thank you for your comment. The committee will consider the benefits associated with this formulation during the evaluation.
	The Royal College of Pathologists	Please see above, related to inclusion age.	Thank you for your comment. The population included in the scope reflects the key clinical trial population, which is expected to inform the marketing authorisation in this indication. The population in the scope has been updated to remove reference to a specific age range, and now refers to children and young people. The committee will be able to make recommendations within the population specified within the marketing authorisation.
	Novartis Pharmaceuticals	The impact on carer should be considered in this evaluation.	Thank you for your comment. Health-related quality of life of carers has

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			been included in the outcomes listed in the scope.
Questions for consultation	The Brain Tumour Charity	The Brain Tumour Charity believe that you should consider a question on quality of life explicitly. Although this may come out in some of the questions on the list, it is important that this is called out for specific consideration.	Thank you for your comment. Health-related quality of life is listed as an outcome. The committee will consider all evidence available to demonstrate the impact that dabrafenib with trametinib has on quality of life.
	Novartis Pharmaceuticals	• **Where do you consider dabrafenib with trametinib will fit into the existing care pathway for i) low-grade glioma and ii) for high-grade glioma?** In line with its marketing authorisation, dabrafenib and trametinib will be used in: • [redacted] • **Which treatments would dabrafenib with trametinib replace? Would it be used instead of or alongside radiotherapy or proton beam therapy, for example?** Dabrafenib and trametinib will not replace radiotherapy or proton beam therapy. We also do not expect dabrafenib and trametinib to be used alongside these therapies as per administered in the trial.	Thank you for your comment.

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		• **Which chemotherapy drugs are used for treatment of low-grade and high-grade glioma in children and young people?** For low grade glioma, the combination of vincristine and carboplatin is the recommended first-line chemotherapy for non-NF1 patients as highlighted in the guidelines for the diagnosis and management of paediatric and adolescent low-grade glioma.[2] For high-grade glioma, there are no defined standard of care for children and young adults. • **Is there unmet need for new treatments for i) low grade-glioma and ii) high-grade glioma?** Patients with glioma, notably those with high-grade have a poor prognosis. There are currently no targeted treatment options for paediatric patients with glioma with a V600E mutation. The availability of dabrafenib with trametinib would give patients a treatment option that could potentially prolong life, reduce morbidity and provide a treatment that can be given orally at home with less healthcare resource utilisation. There is also a large unmet need in paediatric glioma with many patients developing recurrent disease and, in these cases, the therapeutic options are limited, with very few treatments providing clinically meaningful responses.	

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		• **Is it anticipated that dabrafenib with trametinib will offer significant additional benefit over current treatments for i) low-grade glioma and ii) high-grade glioma?** There are currently no NICE recommended treatment for paediatric glioma. Furthermore, evidence from the clinical trial demonstrates a significant improvement in progression-free survival and response rates compared with chemotherapy in patients with low grade glioma. Efficacy data in high-grade glioma also demonstrate a substantial improvement in terms of response rate, progression-free survival and overall survival compared with historical cohorts. Currently, patients with glioma are treated with chemotherapy and are required to attend hospital for a long period of time. This cause stress to children and their carers, as well creating a burden to the NHS. • **Would dabrafenib with trametinib be a candidate for managed access?** We see this as a potential candidate for managed access. • **Do you consider that the use of dabrafenib with trametinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The benefits in quality of life for carers is substantial but may be difficult to capture in the QALY calculation.	

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		Furthermore, compared with chemotherapy that are administered at the hospital, dabrafenib and trametinib are given orally proving significant benefits over current standard of care (reducing burden to the NHS, benefits to patients in terms of time saved and improvement in quality of life). The benefits of an oral treatment, both quantifiable and non-quantifiable, need to be considered as far as possible as part of this appraisal. Furthermore, improving survival for this young population would lead to more patients able to participate to the workforce and society.	
Additional comments on the draft scope	The Brain Tumour Charity	No further comments.	Thank you.
	Novartis Pharmaceuticals	None.	Thank you.

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

None