National Institute for Health and Care Excellence

Health Technology Evaluation

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia

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	Daiichi Sankyo UK Ltd	No comments	No action required.
	Leukaemia Care	N/a	No action required.
	University of Dundee/NHS Tayside (on behalf of RCPath)	The current evaluation through a single technology appraisal is appropriate, and the proposed approach is suitable at this time. It is worth noting that there may be a shift towards a multi-drug appraisal in the future.	No action required.
Wording	Daiichi Sankyo UK Ltd	No comments	No action required.
	Leukaemia Care	Yes	No action required.

Section	Stakeholder	Comments [sic]	Action
	University of Dundee/NHS Tayside (on behalf of RCPath)	Yes, but suggest the use of 'adults with' newly diagnosed FLT3-ITD positive acute myeloid leukaemia to clarify the target population of interest.	Thank you for your comment. The population is kept broad in the scope. Quizartinib will be appraised within its marketing authorisation. No action required.
Timing	Daiichi Sankyo UK Ltd	• Daiichi Sankyo consider it is important for NICE to evaluate quizartinib in a timely manner, in order to provide acute myeloid leukaemia (AML) patients with access to the first FMS-like tyrosine kinase 3 (FLT3) inhibitor specific to the internal tandem duplication positive (ITD+) population. • FLT3-ITD+ AML cases comprise 25% of all AML cases and 75% of FLT3+ cases. These patients have a worse prognosis compared to patients with FLT3-ITD negative AML or FLT3-tyrosine kinase domain positive (TKD+) AML (1, 2). • Oral quizartinib is highly specific to FLT3-ITD with very limited off-target activity compared with first-generation, type I inhibitors (such as midostaurin), which are nonspecific and target other receptor tyrosine kinases involved in the pathogenesis of AML (3). Approximately 40% of patients treated with midostaurin in the first-line setting for FLT3+ AML relapse within 2 years (4), highlighting an unmet need for alternative novel treatment options for this population. • If licensed, quizartinib, when combined with standard induction and consolidation therapy and continued for up to 3 years as a single agent, will represent an effective new treatment option for adult patients with newly diagnosed FLT3-ITD+ AML and has reduced the risk of death by	Thank you for your comment. This topic has been scheduled into the technology appraisal work programme with the aim of providing timely guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. No action required.

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		22% and prolonged median overall survival by 16.8 months compared with placebo (median overall survival [OS]: 31.9 vs 15.1 months, hazard ratio: 0.78 [95% confidence interval: 0.62-0.98, p-value: 0.032]) in the phase 3 QuANTUM-First study (5).	
	Leukaemia Care	N/a	No action required.
	University of Dundee/NHS Tayside (on behalf of RCPath)	The urgency of this STA is fairly high due to the impending regulatory approval of the product/marketing authorisation.	Thank you for your comment. This topic has been scheduled into the technology appraisal work programme with the aim of providing timely guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Daiichi Sankyo UK Ltd	The cornerstone of induction treatment in AML patients deemed fit for intensive chemotherapy is a daunorubicin and cytarabine-based schedule and only patients treated with conventional daunorubicin plus cytarabine	Thank you for your comment. The comparators listed

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		induction regimens and high-dose cytarabine consolidation are eligible for treatment with midostaurin (in the case of FLT3+) (Reference 3 of the draft scope; pan-London guidelines (6)); other options included in the draft scope (e.g. etoposide, amsacrine and mitoxantrone) are alternative formulations in the treatment of the AML population. Daiichi Sankyo suggest updating this section to only include treatments that are specific to the FLT3+ AML population which are more relevant and specific to the decision problem.	in the scope aim to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee. No action needed.
	Jazz Pharmaceuticals	The background section states: "About 25% of people with AML have the FLT3-ITD mutation." Our understanding is that FLT3 is an acquired mutation, but driver mutations may define treatment options over acquired ones. i.e. not all 25% would be quizartinib candidates. The background section states: "For people who are fit enough, intensive treatment is available" which may also drive treatment options with or without the FLT3 (+) mutation and could be a proportion of the 25% population with FLT3-ITD mutation.	Thank you for your comment. Quizartinib will be appraised within its marketing authorisation. No action needed.
	Leukaemia Care	We believe the information to be accurate and complete	Thank you for your comment. No action needed.
	University of Dundee/NHS Tayside (on behalf of RCPath)	Minor comments: 1. Reposition paragraph 3 in 'Background' to include information on the incidence of AML to end of the first paragraph.	Thank you for your comments. The scope typically discusses the nature of the condition, followed

Section	Consultee/ Commentator	Comments [sic]	Action
			by incidence/prevelance and then management. No action needed.
		2. Considering amending the information in paragraph two indicate that the duration of remission and survival is shorter in patients with FLT-ITD AML.	The scope currently notes that “FLT3-ITD-positive AML is associated with a poor prognosis, with people having a lower chance of achieving remission and shorter overall survival”. No action required.
		3. The most commonly used chemotherapy for the induction phase with midostaurin, is cytarabine and daunorubicin.	The scope currently notes that people with a FLT3-ITD mutation are typically offered chemotherapy plus midostaurin and that “the most commonly used chemotherapy regimen for the

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			induction phase is cytarabine and daunorubicin". No action required.
		4. For consolidation, the most commonly used chemotherapy regimens are 'higher doses' of cytarabine monotherapy or…..	This sentence has been updated to reflect that high or intermediate dose cytarabine is typically used at this stage.
		5. Following the intensive treatment stage, people who have achieved complete remission.	The sentence has been updated to refer to "people who are in complete remission".
Population	Daiichi Sankyo UK Ltd	No comments	No action required.
	Leukaemia Care	Yes	No action required.

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	University of Dundee/NHS Tayside (on behalf of RCPath)	It would be important to emphasise that this STA is restricted to adults with the disease.	Thank you for your comment. The population is kept broad in the scope. Quizartinib will be appraised within its marketing authorisation. No action required.
Subgroups	Daiichi Sankyo UK Ltd	N/A	No action required.
	Jazz Pharmaceuticals	AML-MRC with FLT3 (+) mutation	Thank you for your comment. It is unlikely that there would be sufficient evidence for this population to consider it as a subgroup in the cost-effectiveness analysis. No action required.
	Leukaemia Care	N/a	No action required.
	University of Dundee/NHS Tayside (on	It would be of interest to consider sub-group analysis for patients ineligible for allogeneic stem cell transplantation.	People who are ineligible for haematopoietic stem

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	behalf of RCPath)		cell transplant has been added as a subgroup.
Comparators	Daiichi Sankyo UK Ltd	In accordance with the anticipated licensed indication and the QuANTUM-First study design, quizartinib is intended to be used in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy (with or without allogenic haematopoietic stem cell transplantation [allo-HSCT]), followed by quizartinib single agent maintenance/continuation therapy. Daiichi Sankyo intends to present an economic evaluation comparing this regimen to established NHS clinical management without quizartinib (i.e., induction: midostaurin + cytarabine + daunorubicin; consolidation: midostaurin + cytarabine [with or without allo-HSCT]; maintenance: midostaurin monotherapy). The company understanding of the draft scope is that the comparators have been organised and presented according to treatment phase (i.e., induction, consolidation and maintenance) to ensure all possible treatment options are captured in a single treatment continuum. However, if the intended meaning was to evaluate the clinical and cost-effectiveness of quizartinib separately for each treatment phase, we would like to highlight the following challenges: • This does not align with the QUANTUM-First study design and the expected market authorisation (MA) for quizartinib which involved all treatment phases by addition of quizartinib to standard chemotherapy with or without allo-HSCT followed by continuation monotherapy. (Expected indication: [redacted]	Thank you for your comments. The comparators are presented in three sections (induction, consolidation and maintenance) to demonstrate that the treatment options vary by treatment stage. The company is invited to use the modelling approach it feels is most appropriate (while following accepted guidelines and providing clear justification for model structure used). The appraisal committee will consider the appropriateness of the model used.

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		[redacted] (5). • Furthermore, the QUANTUM-First study was not designed to show treatment effect separately for the different treatment phases (primary endpoint is OS from randomisation [i.e., induction] to death due to any cause). The RATIFY trial had a similar design and reported the key outcomes (OS, EFS) across all treatment phases; treatment effects for midostaurin separated for each phase for the population of interest are not publicly available. This presents considerable feasibility challenges to estimate comparative effectiveness by treatment phase. • Finally, this would deviate from precedence and the approach taken in previous NICE Technology Appraisal in this disease area and population, i.e., NICE TA523 for midostaurin (7). **Clarification of HSCT in the treatment pathway** Quizartinib treatment is expected to be used as an addition to standard chemotherapy during induction and consolidation; allo-HSCT, is a procedure undertaken as soon as a complete remission (CR) is achieved and often after one or two cycles of consolidation as a 'holding' measure until the transplant can be performed (6). Therefore HSCT should not be considered a standalone separate comparator to quizartinib, but rather HSCT is an option for eligible patients after they have achieved remission. In the QuANTUM-First study, all eligible patients were allowed to receive allo-HSCT. After consolidation, all patients (including those who received allo-HSCT) were allowed to receive quizartinib monotherapy for up 36 cycles. Therefore, comparators for	Thank you for your comment. People who are ineligible for a haematopoietic stem cell transplant has been added as a subgroup and removed as a comparator.

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		quizartinib need to account for management with and without HSCT to reflect the treatment pathway. Additionally, HSCT was not identified as a separate comparator in the NICE TA523 for midostaurin in untreated FLT3+ AML patients (7). **Removal of the specification of non-routine chemotherapy treatments as comparators** Daiichi Sankyo requests that interventions '*…such as mitoxantrone, etoposide, or amascarine*' are removed as comparators for the following reasons: • There is no NICE guidance supporting the use of these treatments in AML. • These examples do not feature in the clinical guidelines supporting the draft scope. These therapies are recommended, in the reference provided by NICE in the draft scope (6), to be used in '*younger patients with adverse-risk cytogenetics…if there are delays to planned HSCT or if patients are not fit for allograft*'. • There is limited evidence to demonstrate the benefits of using these therapies in FLT3-ITD+ patients. The recommendations referenced by NICE in the draft scope (6, 8) are based on the Burnett et al., 2013 and Burnett et al., 2010 trials, which both enrolled a broader AML population with a low proportion of FLT3-ITD+ patients (9-29%) (9, 10). • No precedence has been identified for the specification of non-routine chemotherapy drugs in prior NICE scopes in this indication, most notably with reference to TA523 (midostaurin) (7).	Thank you for your comment. The comparators listed in the scope aim to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee. No action needed

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		Removal of azacitidine as a comparator Azacitidine is not considered as an appropriate comparator because of the following: • TA827 (azacitidine) states that '*some people with FLT3-mutation-positive AML can have targeted maintenance treatment with midostaurin. Therefore, oral azacitidine would likely be of most benefit to people whose AML does not have an FLT3-mutation*' (11). • Azacitidine is not specific for the FLT3+ mutation. The European LeukemiaNet (ELN) 2022 guideline does not recognise azacitidine as standard treatment in the FLT3+ population, who should be treated with targeted therapy (12). • Azacitidine is only licenced for people not eligible for HSCT in the UK (13). However, quizartinib is suitable in the consolidation/maintenance phase for patients who received intensive chemotherapy regardless of their subsequent eligibility for HSCT. • While it is possible that azacitidine may be used in clinical practice after midostaurin in FLT3+ patients who did not receive HSCT due to a lack of treatment options, such use is not supported by clinical trial data or the identified AML guidelines (4, 12). In addition, the clinical trial of azacitidine begins at the maintenance phase and uses various treatments (not including quizartinib or midostaurin) in the induction and consolidation phases (14). Consequently, any indirect treatment comparison (ITC) conducted using this trial to compare azacitidine with quizartinib and midostaurin would entail significant uncertainty. • Based on the above, Daiichi Sankyo requests that azacitidine is removed from the list of comparators.	Thank you for your comment. The comparators listed in the scope aim to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee. No action needed

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		Daiichi Sankyo suggest the following updates to the comparator section, to ensure a consistent approach is taken to the midostaurin appraisal [TA523]: Comparators: Established clinical management without quizartinib (i.e., induction: midostaurin + cytarabine + daunorubicin; consolidation: midostaurin + cytarabine [with or without allo-HSCT]; maintenance: midostaurin monotherapy)	
	Jazz Pharmaceuticals	Current treatment for newly diagnosed AML with FLT3 (+) mutation and specified by 2022 guidelines is cytarabine + daunorubicin (DA)+ midostaurin so perhaps this should be the comparator for the appraisal of FLT 3 (+) patients. Current treatment option for AML-MRC with or without FLT3 (+) subgroup is Vyxeos liposomal (liposomal cytarabine + daunorubicin) so a comparison between cytarabine + daunorubicin + quizartinib and liposomal Vyxeos in AML-MRC FLT 3 (+) subgroup could also be considered.	Thank you for your comment. The comparators listed in the scope aim to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee. No action needed
	Leukaemia Care	Clinicians advised us that midostaurin is not used as maintenance treatment post haematopoietic/bone marrow transplant as it does not have a licence in this indication. Rather it is used as maintenance treatment in the "chemotherapy-only" patients. This means it is not a direct comparator to quizartinib in the post-transplant indication and this nuance ought to be reflected in the scope and factored in by NICE in this appraisal.	Thank you for your comment. The comparators listed in the scope aim to be inclusive. A rationale should be provided for excluding any comparators from the

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			evidence submission, which can be considered by the appraisal committee. No action needed.
	University of Dundee/NHS Tayside (on behalf of RCPath)	Additional comparators for consideration in induction include Vyxeos (for patients with secondary AML in whom FLT3-ITD may be identified), cyatarabine, daunorubicin and gemtuzumab or FLAG-Ida +/- gemtuzumab, and in the post-transplant setting, off label drugs (e.g sorafenib) and potentially, gilteritinib.	Thank you for your comment. The wording of the comparators section of the scope allows for additional comparators to be included, where relevant. No action needed.
Outcomes	Daiichi Sankyo UK Ltd	Daiichi Sankyo suggest that 'disease-free survival' is revised to 'relapse-free survival' in line with the outcome of the QuANTUM-First trial. According to the ESMO guidelines on clinical trial endpoints these terms can be used synonymously (15). In the QuANTUM-First trial relapse-free survival is defined as 'the time from randomisation, for patients who achieved CR during induction, until the date of documented relapse or death from any cause, whichever occurred first' (5).	Thank you for your comments. Disease free survival has been replaced with relapse free survival.
	Jazz Pharmaceuticals	A suggestion to include: mOS from transplant to death for the subgroup who underwent HSCT or subgroup comparison of mOS of those who did not undergo HSCT, to analyse the contribution to survival of HSCT.	People who are ineligible for HSCT has been added as a subgroup.
	Leukaemia Care	Quizartinib has been studied as maintenance treatment after haematopoietic stem cell transplant/bone marrow transplant as part of the QUANTUM FIRST	People who are ineligible for HSCT has

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		trial. Quizartinib could therefore have the potential to improve or extend the effects of transplant when used as maintenance and this should be considered within the outcome measures.	been added as a subgroup.
	University of Dundee/NHS Tayside (on behalf of RCPath)	Yes, the appropriate outcomes are listed. The inclusion of cumulative incidence of relapse as a separate outcome should be considered.	Thank you for your comment. The company is invited to provide data on additional outcomes where available and relevant.
Equality	Daiichi Sankyo UK Ltd	No comments	No action required.
	Jazz Pharmaceuticals	It is our understanding that the clinical trial was conducted for the age range 18-75. NICE guidance should cover all adults for equality purposes.	Thank you for your comment. Quizartinib will be appraised within its marketing authorisation. No action required.
	Leukaemia Care	We are not aware of any inequality issues for this appraisal.	No action required.
	University of Dundee/NHS Tayside (on behalf of RCPath)	No	No action required.

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Other considerations	Daiichi Sankyo UK Ltd	No comments	No action required.
	Leukaemia Care	N/a	No action required.
	University of Dundee/NHS Tayside (on behalf of RCPath)	None	No action required.
Questions for consultation	Daiichi Sankyo UK Ltd	**Where do you consider quizartinib will fit into the existing care pathway for untreated FLT3-ITD-positive AML?** Quizartinib is expected to fit into the existing care pathway, as a first-line treatment for newly diagnosed adult patients with AML FLT3-ITD+ mutation who are eligible for intensive chemotherapy. It is proposed to be added to standard chemotherapy for induction and consolidation phases, including allo-HSCT, and as monotherapy in the maintenance phase for untreated FLT3-ITD+ AML patients, in accordance with the anticipated licensed indication. **Have all relevant comparators for quizartinib been included in the scope at all three treatment stages (induction, consolidation and maintenance)?** Please see comparator section for further details.	Thank you for your comments. No action required. No action required.

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		Is the technology likely to be similar in its clinical effectiveness and resource use to midostaurin? Or in what way is it different to midostaurin? • Quizartinib, is an oral once-daily, highly potent and selective, second-generation type 2 FLT3 inhibitor, which blocks FLT3-ITD-dependent cell proliferation (see Erba et al., 2023 (5)). It has high binding affinity for FLT3, with a nanomolar affinity of 1.6±0.7 nM (see Zarrinkar et al. 2009 (16)). Midostaurin is a multi-targeted kinase inhibitor with activity against FLT3+ AML. It is a type 1 inhibitor that is essentially ATP-mimetic, inhibiting both ITD and TKD mutations, with a FLT3-ITD IC50 in plasma of 1.700 nM (see Pratz et al. 2010 (17)). • There are no head-to-head studies available comparing quizartinib and midostaurin. An ITC using the QuANTUM-First and RATIFY trial data is currently being conducted subject to an initial feasibility assessment. [redacted] **Will the intervention be used to treat the same population as midostaurin?** The population to be treated with quizartinib encompasses approximately 75% of the FLT3+ population treated with midostaurin. Quizartinib will be used to treat adult patients with newly diagnosed AML with a FLT3-ITD mutation, whereas midostaurin is indicated in AML patients with any FLT3+ mutation, which can be FLT3-ITD or TKD. The presence of FLT3-ITD is a poor prognosis factor and accounts for 25% of all AML cases, while FLT3-TKD mutations are	No action required. No action required.

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		less common, and their significance is not yet completely clear, but they do not appear to be associated with a poor outcome. **Is FLT3-ITD routinely tested for in clinical practice?** Yes, FLT3 testing is standard NHS practice in the UK as part of the diagnostic and risk classification procedure in AML patients (6, 12). It is estimated that testing for the FLT3 mutation occurs in 100% of AML patients, based on clinical expert panel opinion, as described in TA523 (7). **Approximately what proportion of people in complete remission following consolidation therapy would be offered a maintenance treatment? What factors would influence this decision?** • In the QuANTUM-First trial quizartinib or placebo continuation/maintenance therapy was offered to patients after induction and consolidation therapy (including allo-HCT) upon blood count recovery (absolute neutrophil count [ANC] >500 mm³ and platelet count >50 000 mm³ without a platelet transfusion within 24 hours of taking blood samples) (5). • In the QuANTUM-First trial, 67% (116/173) of patients in the quizartinib arm that achieved CR (or composite complete remission) after consolidation proceeded to the continuation phase (5). The main objective of maintenance therapy is to prevent relapse i.e. to decrease relapse risk for a course of time after achievement of CR through long-term, tolerable therapy. **Would quizartinib be a candidate for managed access?**	No action required. No action required. No action required.

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		• The QuANTUM-First trial was powered to observe a meaningful treatment difference in its primary endpoint, OS, between the quizartinib and placebo arms in the intent-to-treat (ITT) population. The OS data from the QuANTUM-First trial is considered to be relatively mature, as the number of patients alive in both treatment arms is less than 50% at the end of the trial follow-up period (median follow-up = 39.2 months) (5). Median overall survival was 31.9 months (95% CI: 21.0-not estimable) for quizartinib versus 15.1 months (95% CI: 13.2-26.2) for placebo, with a hazard ratio for death of 0.78 (95% CI: 0.62-0.98, p-value: 0.032) (5). • There are not any further per protocol defined data collection plans from the QuANTUM-First trial. • It is therefore not likely that this treatment would be a suitable candidate for managed access based on the anticipated data package available at submission and the future data collection plan for this indication. **Do you consider that the use of quizartinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No comments. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** No comments.	No action required. No action required.
	Leukaemia Care	N/a	No action required.

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	University of Dundee/NHS Tayside (on behalf of RCPath)	None	No action required.
Additional comments on the draft scope	University of Dundee/NHS Tayside (on behalf of RCPath)	None	No action required.

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

None.