National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pacritinib for treating myelofibrosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Section	Consultee/ Commentator	Comments	Action
Wording	Royal College of Pathologists/British Society for Haematology	yes	Comment noted. No action required.
	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	Yes, we agree the draft remit reflects the clinical and cost-effectiveness issues required for consideration by NICE.	Comment noted, No action required.
Timing Issues	Royal College of Pathologists/British Society for Haematology	Low to medium urgency	Comment noted. No action required.

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	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	Approximately 25% of patients with myelofibrosis (MF) have a platelet count <100,000/µL, which renders them a high-risk population with short survival and increased symptom burden. Patients with severe thrombocytopenia defined as <50,000/µL are at even higher risk. Patients with low platelet counts are often excluded from clinical studies. In addition, patients who fail ruxolitinib due to intolerance or inadequate response have no approved treatment options. Pacritinib, which displays a lack of myelosuppression and is clinically effective even in patients with cytopenias, and previously treated with ruxolitinib, has been developed to address these unmet needs. Whilst there is considerable unmet need in this patient population this needs to be balanced with NICE's wish to conduct appraisals in as efficient a manner as possible with all relevant data. [redacted]	Comment noted. No action required.

Section	Consultee/ Commentator	Comments	Action
Additional comments on the draft remit	CTI Life Sciences Ltd	No	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Royal College of Pathologists/British Society for Haematology	Main points covered	Comment noted. No action required.
	Celgene	**Please provide clarity in relation to the following comment:** "Between 25% of people with myelofibrosis develop acute myeloid leukaemia.1" As MF continues to advance, patients are at increased risk of evolution to acute myeloid leukaemia (AML), reported to occur in 8−23% of patients within 10 years from diagnosis.1 Median OS following transformation to AML is approximately 3 months according to a study involving 91 cases of leukaemic transformation.1 As such, Celgene suggests presenting a range. Reference: 1. Mesa RA, Li CY, Ketterling RP et al. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 cases. Blood 2005;105:973–7. **Please provide clarity in relation to the following comment:**	Thank you for your comment, the background section is intended to provide a brief summary of myelofibrosis. It has been amended to include a range for the proportion of people with myelofibrosis that develop acute myeloid leukaemia. The incidence of myelofibrosis has also been amended and a

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		"The annual incidence of myelofibrosis is approximately 0.75 per 100,000." Is this a UK specific incidence rate? **Please include the following:** In addition to the prognostic factors outlined in the draft scope, mutational status should also be included as it is increasingly taken into account when considering the prognosis of patients with myelofibrosis.2 Reference: 2. Vannucchi AM, et al. Leukemia 2013 Sep;27(9):1861-9.	reference has been added for clarity.
	CTI Life Sciences Ltd	The information provided is both accurate and comprehensive. There is one wording correction that we propose to amend: "Between 25% of people with myelofibrosis develop acute myeloid leukaemia" should be changed to "Up to 25% of people with myelofibrosis develop acute myeloid leukaemia". We are unclear on the source of the 25% figure. However we are concerned that this may be too high, based on a 2012 study of primary myelofibrosis patients by Cervantes and Pereira, which suggested the rate to be between 10% and 20%.1 The draft scope currently states "The median survival is 5 years from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival." However, since thrombocytopenia is a negative prognostic factor for OS in patients with MF, we feel it would be useful to highlight the median survival for the target population. For example, a retrospective cohort of 1109 patients in the US indicates a median OS of 33.8 months for patients with platelets between 50,000 µL to 100,000/µL and 14.7 months for patients <50,000/µL.2	Thank you for your comment, the background section is intended to provide a brief summary of myelofibrosis. It has been amended to include a range for the proportion of people with myelofibrosis that develop acute myeloid leukaemia.

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The technology/ intervention	Royal College of Pathologists/British Society for Haematology	Yes, but could be expanded by more than one sentence. Could include something on the mechanism of action.	Thank you for your comment, the technology section has been amended.
	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	Yes Suggest wording “Pacritinib, is a novel multi-kinase inhibitor against JAK2/FLT3/IRAK1 with negligible activity against JAK1.	Thank you for your comment, the technology section has been amended.
Population	Royal College of Pathologists/British Society for Haematology	The draft does not specify whether Pacritinib is being considered as alternate to Ruxolitinb as first line therapy or for subgroups with low blood counts or for those refractory/intolerant to ruxolitinib as 2nd line therapy. The latter 2 special groups may benefit more from pacritinib. From reading the draft it seems to cover all these indications.	Thank you for your comment, additional subgroups have been added to ‘other considerations’.
	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	The anticipated license is for treatment of disease-related splenomegaly and control of symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF) who have thrombocytopenia (platelet counts ≤100,000/μL). The license application reflects the trial evidence. PERSIST 1 successfully demonstrated that pacritinib can not only be safely administered and clinically effective in patients with MF with normal platelet	Thank you for your comment, additional subgroups have been added to ‘other considerations’.

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		counts, but patients with thrombocytopenia (platelet counts <100,000/μL) also displayed clinically meaningful positive results. Therefore, a phase 3 study (PERSIST-2) was conducted to confirm efficacy in participants with thrombocytopenia, where there exists a significant unmet need due to the lack of evidence for the currently approved JAK inhibitor, which is known to be myelosuppressive. Relevant subgroups in addition to those listed in other considerations are: • Prior treatment with JAK2 inhibitors • Patients with severe thrombocytopenia (defined as platelet count <50,000/μL) • Primary vs. secondary MF • Haemoglobin (>10/μL or <10/μL) • Patients dependent on RBC transfusion	
Comparators	Royal College of Pathologists/British Society for Haematology	The direct comparator should be ruxolitinib.	Comment noted. No action required.
	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	Given the wide variety of regimens used in clinical practice and the palliative nature of these treatments it is proposed to consider the comparator as a basket therapy, referred to as best available therapy (BAT). We believe that ruxolitinib and BAT describe current UK clinical practice among myelofibrosis patients. The figure below describes our current	Thank you for your comment, the treatments listed as part of established clinical practice are examples and are not intended to

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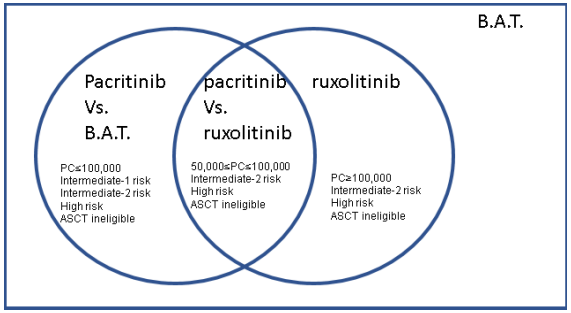
		understanding of current clinical guidance from NICE on front line treatment of MF, and the position which pacritinib may take.  There are no approved therapies for thrombocytopenic patients (<100,000/μL) intolerant or resistant to ruxolitinib (2nd line therapy) and therefore BAT would be an appropriate comparator. Although allogeneic stem cell transplant (ASCT) is considered the only potentially curative treatment for myelofibrosis, we do not consider it to be a direct comparator to pacritinib, through its position in BAT for two primary reasons. Firstly, ASCT is rare in clinical practice, a justification used to not consider ASCT within the ruxolitinib submission to NICE (TA386), which was not challenged by the NICE committee or the ERG. Secondly, both the inclusion criteria for PERSIST- 2 and the expected license for pacritinib include a restriction based on ineligibility for or history of ASCT.	be an exhaustive list. The specific population eligible for treatment with ruxolitinib has been added in line with NICE TA386 Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis.

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		Ruxolitinib is recommended by NICE and is considered separate to the other therapies within the BAT basket because it is a targeted therapy, rather than a treatment for symptom control. Within the sub-populations for which ruxolitinib is currently recommended by NICE, ruxolitinib is considered the best alternative care (see diagram). However, ruxolitinib is not indicated for myelofibrosis patients with platelet counts of <50,000/μL and is not recommended by NICE for intermediate-1 risk category patients. For these sub-populations, BAT is the best alternative therapy, and will be considered the only comparator to pacritinib. There are 3 different methods available for measurement of risk level in myelofibrosis, IPSS was used in the COMFORT trials for ruxolitinib and is the basis of the existing recommendation. The subsequent DIPSS increases the importance of anemia as a prognostic factor and is what is used within the PERSIST 2 trial for pacritinib. The newly developed DIPSS Plus score incorporates the same factors as the IPSS with an additional 3 variables for improved prognostic categorization (red cell transfusion need, thrombocytopenia, and “unfavorable” karyotype). As risk is scored differently across trials and in clinical practice the use of risk level to determine comparison to ruxolitinib may be difficult and we would appreciate advice on this. Finally, we do not consider splenectomy (within established clinical practice) to be a comparator to pacritinib, since it is rarely performed in this indication.	
Outcomes	Royal College of Pathologists/British Society for Haematology	Yes. If possible it should look at the effect on 1. blood counts 2. allele burden of the JAK2/CALR/mpl mutations, and on 3. the degree of myelofibrosis.	Thank you for your comments. Hematologic parameters (including red blood cell transfusion and blood count) have been

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		Adverse events may be expanded to specifically cover bleeding and heart disease. The drug was put temporarily on clinical halt by FDA due to increased death from haemorrhage and heart failure.	added to the list of outcomes.
	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	We agree that these are appropriate outcome measures for MF, and notably have been included in previous appraisals of interventions in myelofibrosis (e.g. TA386 for ruxolitinib). They are also in line with the study design for PERSIST-1 and 2. However, given the risk of anaemia in the target population, we would also like to include red blood cell (RBC) transfusion as an outcome measure.	Thank you for your comments. Hematologic parameters (including red blood cell transfusion and blood count) have been added to the list of outcomes.
Economic analysis	Celgene	No comment	Comment noted. No action required.
	CTI Life Sciences Ltd	We agree with the points made in the draft scope. The appropriate time horizon is expected to be lifetime.	Comment noted. No action required.
Equality and Diversity	Celgene	No comment	Comment noted, No action required.
	CTI Life Sciences Ltd	There are no specific equality issues of which we are aware.	Comment noted. No action required.
Other considerations	Celgene	No comment	Comment noted. No action required.

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	CTI Life Sciences Ltd	There are no further considerations beyond the points made in the draft scope.	Comment noted. No action required.
Innovation	Royal College of Pathologists/British Society for Haematology	The technology would benefit patients with low platelet counts where Ruxolitinib is contraindicated, and patients who are refractory to or intolerant of ruxolitinib. These patients would otherwise be left without disease-specific therapy. The improvement in the quality of life & symptom relief should benefit significantly patients with myelofibrosis, but this would not be part of QALY calculations As far as I am aware, there is trial data on safety, dosing and efficacy vs. BAT, data on efficacy in patients with low platelet counts, and on patients intolerant/refractory to ruxolitinb. I believe there is no direct comparison between ruxolitinib and pacritinib. See PERSIST 1 and 2 trials.	Comment noted. The potential innovative nature of the technology will be considered by the appraisal committee. No change to the scope required.
	Celgene	No comment	Comment noted. The potential innovative nature of the technology will be considered by the appraisal committee. No change to the scope required.
	CTI Life Sciences Ltd	Pacritinib is an innovative technology with clear benefits for MF patients with cytopenias and treated with prior JAK inhibitor therapy. Pacritinib, is a novel multi-kinase inhibitor against JAK2/FLT3/IRAK1 with negligible activity against JAK1. Unlike ruxolinitib (JAK1/JAK2 inhibitor), treatment with pacritinib leads to minimal myelosuppression. As a result,	Comment noted. The potential innovative nature of the technology will be considered by the appraisal

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		pacritinib provides a treatment option for cytopaenic myelofibrosis patients, who would be ineligible for ruxolitinib and otherwise limited to BAT, and patients treated with prior JAK inhibitor therapy. Pacritinib therefore represents a step change in the management of myelofibrosis for patients who may require extensive care from family members, impacting the health-related quality of life of informal carers. There is also evidence to suggest pacritinib reduces the need for RBC transfusion in patients with MF. Transfusion therapy is a core strategy for treatment of disease-related anaemia and is also used to manage thrombocytopenia. However, blood transfusion is both a scarce and costly resource, as well as an invasive procedure for the patient. Therefore, a reduction in RBC transfusions offers benefit to patients and the NHS. Finally, some treatments which form part of BAT are administered intravenously. The benefit of an oral therapy like pacritinib as a substitute for these may be significant. CTI are currently undertaking a systematic literature review to establish the data which may be available to capture the impact of these factors.	committee. No change to the scope required.
Questions for consultation	Celgene	No comment	Noted.
	CTI Life Sciences Ltd	Q. Is the population defined in the scope appropriate? A. Please see comments in the section “Population” Q. Have all relevant comparators for pacritinib been included in the scope? A. Please see comments in the section “Comparator” Q. Which treatments are considered to be established clinical practice in the NHS for myelofibrosis (both primary and secondary)?	Comments noted. Please see NICE’s responses to comments on the population and comparators as above,

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		A. The comparators that are listed in the draft scope are those considered to be established clinical practice. Please see the population and comparators cells above for further description. Q. How should established clinical practice be defined? A. Please see the population and comparators cells above. Q. Is best supportive care appropriately defined? A. Please see the population and comparators cells above.	Comment noted
		Q. Would treatment with pacritinib be considered only for people for whom haematopoietic stem cell transplant is inappropriate? A. Yes, in line with the inclusion criteria of the PERSIST-1 and 2 trials, and the expected license for pacritinib. ASCT is considered a potentially curative therapy. Therefore, it is understood that if patients meet the eligibility criteria for treatment, they will not be considered for pacritinib therapy.	Comments noted. No action required.
		Q. Will pacritinib be used to treat myelofibrosis or the symptoms of myelofibrosis? A. The impact of pacritinib therapy on the underlying disease is still being explored and is unclear. Pacritinib therapy is used to treat the symptoms of MF.	Comments noted, Please see NICE's responses to comments on outcomes, subgroups, population, comparators, and innovation as above.
		Q. Are the outcomes listed appropriate? Are the subgroups suggested in other considerations appropriate? Are there any other subgroups of people in whom pacritinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? A. See the outcomes cell above. We also propose the following subgroups: • Prior treatment with JAK2 inhibitors	

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		• Patients with severe thrombocytopenia (defined as platelet count <50,000/μL) • Primary vs. secondary MF • Haemoglobin (>10/μL or <10/μL) • Patients dependent on RBC transfusion Q. Where do you consider pacritinib will fit into the existing NICE pathway, Blood and bone marrow cancers? A. See above answers that define patient population for pacritinib. Also see diagram in comparators section. Q. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. A. We are not currently aware of such evidence. Q. Do you consider pacritinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A. Yes. Answered previously. Q. Do you consider that the use of pacritinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. A. Yes. Answered previously.	Comments noted. No action required.

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		Q. Would it be appropriate to use the cost comparison methodology for this topic? A. Pacritinib may be licensed for a wider indication than ruxolitinib. Therefore, the intended positioning of pacritinib is such that it will replace BAT for some patients (those with platelet counts <50,000/μL, or categorised as intermediate-1 risk, or ruxolitinib failures), and ruxolitinib for all other eligible patients. Cost comparison would be suitable versus ruxolitinib but not versus BAT. Q. Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? A. There is expected to be similarity to ruxolitinib therapy at its approved starting dose of 15mg to 20mg BID. Q. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? A. Yes. The efficacy coprimary endpoints were: • Proportion of patients achieving 35% or more spleen volume reduction (SVR) assessed by computed tomography/magnetic resonance imaging (CT/MRI) • 50% or more reduction in total symptom score (TSS) according to the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAFTSS 2.0) from baseline to week 24. To our knowledge the endpoints included in the PERSIST-2 trial are still clinically relevant. Q. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?	

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		A. We are not aware of new evidence for the comparator technology or any important ongoing trials. CTI is currently conducting the PAC203 study in patients previously treated with ruxolitinib.	

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

BMS, Leukaemia Care