National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

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 [sic]	Action
Appropriateness	MPN Voice & Leukaemia Care	The evaluation of momelotinib is important because of the unmet needs of a significant proportion of myelofibrosis patients. We agree that the STA evaluation process is appropriate.	Thank you for your comment. This evaluation has been scheduled into the work programme as a Single Technology Appraisal.
	GSK	This topic should be referred to NICE as a matter of urgency due to the high unmet need in patients with myelofibrosis, who have poor survival outcomes and diminished quality of life.[1,2] GSK agree that a single technology appraisal is the correct route for evaluation of momelotinib.	Thank you for your comment. This evaluation has been scheduled into the work programme as a Single Technology Appraisal.
Wording	MPN Voice & Leukaemia Care	The importance of this evaluation is the prospect of a new drug becoming available for MF patients for whom existing treatments are unsuitable or ineffective. Could the following paragraph be inserted directly above the heading “The Technology”, to emphasise the point?	Thank you for your comment. This evaluation has been scheduled into the work programme.

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		Patients for whom the first line therapy, ruxolitinib either cannot be used or is ineffective have very limited therapeutic options. In particular, anaemic patients need a more effective drug to be made available.	The background section aims to provide a brief summary of the disease and how it is managed. The available treatment options are discussed. No change to the scope needed.
Timing Issues	MPN Voice & Leukaemia Care	There are unmet needs for a significant proportion of MF patients, so other treatment options are needed as soon as possible.	Thank you for your comment.
	GSK	Adult patients with myelofibrosis-related splenomegaly and symptoms of disease, including anaemia, have poor outcomes and quality of life.[1,2] It is therefore important that patients have access to momelotinib at the earliest possible opportunity. Specifically; • Patients suffering from suboptimal management through the existing standard of care are forced to tolerate this because of paucity of suitable treatments for Janus kinase inhibitor (JAKi)-exposed patients. Additional treatment options are required for JAKi-naïve patients. Current JAKi are not suitable for all patients and have the potential to cause haematological toxicities in already ill patient groups.	Thank you for your comment. This evaluation has been scheduled into the work programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MPN Voice & Leukaemia Care	Apart from the above comment concerning unmet needs, no other comment	Thank you for your comment.
	GSK	While the background information provides a useful overview of the condition and available treatments, GSK believe that it fails to capture the impact of the disease on patients and unmet need, particularly for those classified as intermediate 2 and those at high-risk. These patients constitute approximately 50% of those with myleofibrosis and have very limited survival expectancy (as limited as approximately 2 years in high-risk patients).[2,3] Information regarding survival in myelofibrosis patients was included in the background of the scope of TA386 assessing ruxolitinib. In addition, between one-third and half of patients have anaemia at diagnosis with approximately one-third requiring transfusion during the course of their disease.[3] Severe anaemia and transfusion dependence are associated with increased risk of death in myelofibrosis patients.[4,5] Therefore, the unmet need is particularly acute in these patients. Lastly, though risk groups are important factors in guiding treatment, they are not the only consideration; guidelines also advise assessing the expected benefit and risk of toxicity with available treatments.[6] This has led to approximately half of UK myelofibrosis patients in higher risk groups being observed rather than actively treated.[3]	Thank you for your comment. The background section is intended to be a brief introduction to the condition and treatment options, therefore the level of detail listed here has not been included in the scope. However, the background section has been updated to include information on the median survival for people with myelofibrosis, to specify that risk categorisation can *help* guide treatment and that limited treatment options are available for some people.
Population *Is the population defined appropriately?*	MPN Voice & Leukaemia Care	Yes	Thank you for your comment.

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Subgroups	MPN Voice & Leukaemia Care	Apart from the above comment concerning unmet need, no other comment	Thank you for your comment.
	GSK	While GSK acknowledge the prognostic criteria detailed in the draft scope are important, we do not believe it is appropriate to have separate subgroup analyses based on individual prognostic factors such as presence or absence of symptoms or platelet count. Such factors are considered within prognostic scoring tools for predicting survival in patients with Myelofibrosis.[7,8] Guidelines regarding the use of JAKi therapies do not recommend consideration of these prognostic factors in isolation with regards to initiating therapy. Clinical decision making in the UK is based on a holistic assessment of disease presentation and the existence of symptoms which impinge on quality of life, per British Society for Haematology (BCSH) guidelines.[9,10] As noted above, the anticipated marketing authorisation of momelotinib is expected to be for use in patients who are JAKi naïve or have been treated with a JAKi and the economic case will include subgroup analyses for each of these groups.	Thank you for your comment. The subgroups listed are consistent with subgroups listed in previous scopes in this disease area. The committee will consider subgroup analysis presented for groups which are clinically identifiable. The company should include analysis for any other subgroups it believes appropriate in its submission and provide evidence for their relevance. The company should also explain in its submission why analysis for any subgroups listed in the scope are not provided. No changes to the scope are needed.

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Comparators *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?*	MPN Voice & Leukaemia Care	Yes	Thank you for your comment.

	GSK	BCSH guidelines and clinical expert feedback indicate that patients may continue to be treated with JAKi (i.e., ruxolitinib), even despite inadequate response, and despite adverse effects and myelosuppression.[9,10] This is not accounted for in the current comparator scope.
		GSK believes an appropriate list of comparators is as follows:
		• For people with no previous treatment with JAKi and intermediate-2 or high-risk disease:
		  o ruxolitinib
		• Patients with prior JAKi exposure, who may be currently receiving JAKi or have discontinued but remain eligible for JAKi treatment
		  o established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion) +/- ruxolitinib
		• For people contraindicated to ruxolitinib or if ruxolitinib is not appropriate:
		established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion)
			Thank you for your comment. The comparators have been updated to include ruxolitinib as a comparator for people eligible for ruxolitinib.

Outcomes *Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and*	MPN Voice & Leukaemia Care	Yes	Thank you for your comment.
	GSK	While progression-free survival (PFS) has been included in relevant prior technology appraisal scopes, GSK do not believe that it is considered a clinically relevant endpoint for patients with myelofibrosis. Revised response	Thank you for your comment. Progression-

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harms) of the technology?		criteria for myelofibrosis published in 2013 by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) included additional clinical trial response categories to assess activity in alleviating anaemia, splenic, discomfort, and constitutional symptoms.[11] Though assessment of progression was included, PFS was not a recommended response criterion. The cost-effectiveness model will primarily be informed by the key clinical efficacy measures of anaemia and transfusion dependence and will include overall survival. In addition to overall survival, leukaemia-free survival was an endpoint in momelotinib clinical trials and will be reported in the submission.	free survival has been removed as an outcome from the scope and leukaemia-free survival has been added.
Equality and Diversity	GSK	Though use of momelotinib should not be restricted by age, and is not anticipated to be in the product label, it is of clinical interest that age (age >65 years old) is a prognostic factor in myelofibrosis.2 Age is one of the protected characteristics under the Equality Act 2010. The scope, and wider appraisal process, should be mindful not to unduly limit access to momelotinib in patients based on their age. We do not envisage any other equality issues arising from the proposed remit and scope.	Thank you for your comment. This potential equalities issue has been noted in the equality impact assessment.
Other considerations	GSK	Momelotinib is the only JAKi that targets JAK1, JAK2 and regulates iron metabolism via inhibition of ACVR1/ALK2.[12] Due to its mechanism of action, momelotinib has shown benefits in reducing burden of anaemia in patients with myelofibrosis, including helping more patients achieve or maintain transfusion independence compared with best supportive care +/- JAKi in JAKi naïve and JAKi experienced patients.[13,14] Other commonly used JAKis target only JAK-STAT signalling pathways and tend to exacerbate anaemia in patients with myelofibrosis.[12] Therefore, this will be a first-in-class submission. GSK aim to demonstrate that momelotinib will improve NHS treatment of myelofibrosis by offering a	Thank you for your comment. No changes to the scope are needed.

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		different option to clinicians. This system-level improvement should also be considered in the appraisal.	
Questions for consultation	GSK	• *Where do you consider momelotinib will fit into the existing care pathway for myelofibrosis?* GSK considers that the momelotinib would treat patients with splenomegaly and/or symptoms of myelofibrosis who have not been treated with a JAKi treatment (i.e., no previous treatment with ruxolitinib and intermediate-2 or high-risk disease). For indicated patients who have been exposed to JAKi, momelotinib may be appropriately positioned for patients who have not responded or are no longer responding to other JAKi, and those not tolerating or poorly tolerating other JAKi treatment. Momelotinib would be used prior to established clinical practice in indicated patients who are contraindicated to JAKi or if JAKi is not appropriate. • *Would momelotinib be a candidate for managed access?* GSK are unable to speculate on whether there will be uncertainty in the clinical or cost-effectiveness of momelotinib which could be addressed through entry into managed access. All three pivotal trials for momelotinib in myelofibrosis have completed and will be fully reported in the submission. • *Do you consider that the use of momelotinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*	Thank you for your comments. No changes to the scope are needed.

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		It is not yet known whether momelotinib will provide HRQoL benefits which are not adequately captured in the QALY calculation. However, fatigue is a common symptom experienced by patients with myelofibrosis that may be improved by momelotinib treatment. Fatigue is known to be captured inadequately by generic utility measures and therefore underrepresented in QALY estimates.[15,16] GSK will report all relevant patient-reported outcomes captured during clinical trials to allow consideration of momelotinib's beneficial effects. • *Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* N/A. • *Would it be appropriate to use the cost-comparison methodology for this topic?* While the most appropriate modelling methodology has not yet been determined, GSK believe that cost-comparison is an appropriate potential methodology for consideration in some populations. • *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* GSK believe that momelotinib has demonstrated similar clinical efficacy to the most appropriate comparators, including ruxolitinib (in the SIMPLIFY-1 trial).[10] While resource use is still to be determined within the economic case, it is likely that overall resource use will favour momelotinib due to the	

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		reduction in requirement for transfusion demonstrated in the clinical trial program for both JAKi naïve patients and JAKi-experienced patients compared with best supportive care +/- JAKi.[10,11] • *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* Yes. The primary endpoint in the phase III SIMPLIFY-1 and -2 trials was splenic reduction (≥35%) at week 24. This is a clinically relevant endpoint and matches that of key clinical trials of ruxolitinib considered in TA386. A third relevant phase III trial (MOMENTUM), that will be fully reported in the submission, used a primary endpoint (difference in Myelofibrosis Symptom Assessment Form total symptom score response at week 24) that has not been included in the relevant outcomes listed in the scope above. However, key secondary outcomes were relevant. • *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?* No substantial new evidence will be available from any momelotinib trial in 2023.	

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

Novartis