National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Bosutinib for untreated chronic myeloid leukaemia

Response to consultee and commentator 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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	To be clear and unambiguous on the line of therapy as well as patient group, we suggest to specify the wording to "[...] bosutinib within its marketing authorisation for treating newly diagnosed chronic phase chronic myeloid leukaemia". Besides being licensed for chronic phase CML, the marketing autorisation also licenses bosutinib for accelerated phase and blast phase CML - two phases that are not included in the planned appraisal.	Comments noted. The line of therapy and patient group is further specified in the 'population' section of the table in the scope. No changes to the scope are needed.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	The wording is correct	Comment noted. No changes to the scope are needed.

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Timing Issues	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	We have no comments regarding the timing of this appraisal.	Comment noted. No changes to the scope are needed. An appraisal of bosutinib has been scheduled into NICE's technology appraisal work programme.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	There is no immediacy for the appraisal as other treatment options are available to patients with newly diagnosed CML. However for any particular patient, the option to start bosutinib would be helpful so that they are not required to cycle through sub-optimal treatment or treatment that would be likely to induce a side-effect. This would maximise response, and minimise intervention for side-effects of therapy.	Comments noted. No changes to the scope are needed. An appraisal of bosutinib has been scheduled into NICE's technology appraisal work programme.
Additional comments on the draft remit	ACP-NCRI CML Working Party-RCP-RCPath-BSH	A valuable submission which will improve patient care through the availability of tailored cancer therapy	Comment noted. No changes to the scope are needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	CML is no longer a three phase disease with a 4 year median survival. Real World Data shows that with current treatments available there is a 97% chance of patients diagnosed today living to their normal life expectancy.	Comments noted. The background section is intended to provide a brief overview of the disease and its associated management. No changes to the scope are needed.
	Bristol-Myers Squibb	All background information appeared accurate on our review.	Comment noted. No changes to the scope are needed.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	The background information is accurate. However it is essential that patients presenting with more advanced forms of CML (accelerate and blast phase) have access to the more potent second generation TKIs (2G-TKIs). I have expanded on the background. In order for chronic myeloid leukaemia (CML) patients to be treated with the highest quality of care and not to offer a sub-standard level of management, inferior to many other European countries, impacting on patient outcome and quality of life, TKIs should be used within their licensed indications. Bosutinib first line therapy should be available for the same indications that NICE approved nilotinib and then dasatinib. Since the concept of first line second generation TKI use has already been approved and recognised by NICE (in the case for the other second generations TKIs, nilotinib and dasatinib), this appraisal will focus on the differential benefits of bosutinib first line. As NICE has already approved up-front second generation TKI use, this concept will not be expanded on in this submission.	Comments noted. The background section is intended to provide a brief overview of the disease and its associated management. No changes to the scope are needed.

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		Modern management of CML within the NHS is with tyrosine kinase inhibitor (TKI) therapy, directed by haematologists. Until now, three TKIs were licensed first line for CML: imatinib and the second generation drugs: dasatinib and nilotinib. Bosutinib has now successfully completed a trial for first line therapy at present against imatinib, showing improved responses, in a very similar way to the other second generation drugs (2G-TKI). CML is a tri-phasic disease comprising of chronic, accelerated and often terminal blast phase. Chronic and accelerated phase CML Imatinib, nilotinib and dasatinib are approved for first line therapy for CML in chronic and accelerated phase by NICE. Blast phase CML With the exception of nilotinib, all other TKIs are licensed for the more aggressive and highly refractory blast phase of CML. It is essential that physicians continue to have access to more potent drugs than imatinib for effective treatment of more advanced phase CML which if terminal if not managed appropriately. In case of intolerance, physicians should be able to change therapy to another more potent, but better tolerated TKI. There should not be a significant geographical variation, as therapy follows the recommendations published and updated by the European LeukaemiaNet. Both the European ELN guidelines and the NCCN American guidelines clearly recommend all licensed TKIs for first line therapy and do not discriminate between them. Similarly, there should not be a difference in opinion between specialists as most accept the recommendations outlined by the ELN. These guidelines will be updated as the TKIs expand their licence. The new UK BSH and LCA guidelines will incorporate a recommendation for bosutinib for first line use, within its licence. Alternatives to NICE approved first line TKIs have been clinical trials. In the UK, the SPIRIT-2 NCRI study (now completed) compared first line imatinib	

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		with first line dasatinib; the commercial Avillion sponsored CML study (now completed) compared first line imatinib with Bosutinib. There is no current trial for newly diagnosed CML patients. Although nearly 80% of patients will achieve clinical responses on imatinib, after 8 years of therapy, only half of these patients will still be receiving imatinib due to failure of the drug due to resistance or intolerance. More patients will achieve faster and more potent clinical responses on second generation drugs (nilotinib/dasatinib/bosutinib) up front, but these may also be associated with side-effects effects of therapy, causing patients to discontinue for intolerance rather than resistance. The benefit of giving 2nd generation TKIs upfront is the advantage of earlier responses reducing the risk of progression to advanced phase CML. There is a significant reduction in progression to advanced phase CML in the first 2 years compared to imatinib. Patients with chronic phase CML can be stratified according to their risk of progression by their Sokal risk score. Patients with a high Sokal score are traditionally predicted to have a worse outcome and these patients should have the opportunity to be treated with a more potent 2nd generation drug upfront, with equal access to all 2G-TKIs. Patients in advanced phase need to be treated more aggressively upfront to prevent disease progression, and these patients should have equal access to 2nd generation drugs up-front. The advantage of a deeper response is that more patients will become eligible to stop TKI medication in the future. Only patients that have achieved deep molecular responses (Complete molecular response (4-4.5 log reduction, quantitative PCR for BCR-ABL of < 0.01% on the International scale (IS)) are currently eligible for stopping studies. Trials of stopping TKI are also in place for patients in a major molecular response (MMR, quantitative PCR of < 0.1% on the IS). Far greater number of patients achieve MMR and CMR on 2nd generation drugs (bosutinib, dasatinib, nilotinib). For patients on therapy for 5 years with a DMR for 2 years, there is an opportunity to stop therapy. Clinical trials show that 60% of such patients mange to stay	

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		off their medication long term (follow up of 10 years). Twice as many patients treated with up front 2G-TKI will be eligible for a trial of stopping in comparison to imatinib. This has a considerable impact not only for health-economic considerations, but will also spare patients any long-term side-effects of therapy.	
The technology/ intervention	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	Yes.	Comment noted. No changes to the scope are needed.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	Yes.	Comment noted. No changes to the scope are needed.
Population	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	We agree on the population stated.	Comment noted. No changes to the scope are needed.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	The population is defined appropriately, and is the same population that was considered for first line nilotinib and dasatinib, which are both NICE approved. Special groups that should be considered are those patients with specific co-morbidities and high risk CML, where giving nilotinib or dasatinib may be detrimental.	Comments noted. No changes to the scope are needed.
Comparators	Pfizer	No comments.	Noted.

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	Bristol-Myers Squibb	We agree on the comparators listed. An appropriate (indirect) comparison with all comparators will need to be provided, since trial evidence only covers a direct comparison with imatinib.	Comments noted. No changes to the scope are needed.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	The true comparators of bosutinib first line, would be another first line 2G-TKI, either nilotinib or dasatinib. First line nilotinib has a number of practical concerns- it needs to be given twice a day, with a 3 hour fast for each medication, which has issues with drug compliance. Nilotinib also has a distinct side-effect profile: – aggravates diabetes – causes glucose intolerance leading to 25% of patients having indices within the diabetic range within 5 years of nilotinib therapy – increases the cholesterol levels in patients – is associated with cardio-vascular (CV) thrombotic events, which by definition are irreversible. These arterio-thrombotic side-effects are more prevalent in patients with pre-existing CV risk factors. Dasatinib also has a unique side-effect profile and is associated with a cumulative incidence of pleural effusion of 30-40%. CV side-effects include the development of pulmonary arterial hypertension (PAH), which again is irreversible. Patients with pre-existing cardiac disease, CV risk-factors, pleural effusions at baseline, should have the opportunity to be treated with other TKIs that will not aggravate their co-morbidities, and lead to further medical intervention and treatment discontinuation. Despite the requirement to prevent progression and to attempt to achieve deeper molecular responses on 2nd generation drugs in order to stop future TKI therapy, all haematologists would avoid giving nilotinib to high CV risk patients. A preference for the NICE approved 2nd generation TKI approach upfront would be an alternative 2nd	Comments noted. The side-effect profiles of bosutinib and comparators will be considered as part of the appraisal. No changes to the scope are needed.

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		generation TKI in order not to inflict an arteriothrombotic event to a patient already at risk of developing this event. Bosutinib is not known to be associated with conventional arteriothrombotic events, typically myocardial infarction, stroke and peripheral arterial occlusive disease. Bosutinib has a very similar CV profile to imatinib, unlike nilotinib and dasatinib. Patient groups that would be specifically discriminated against if 1st line bosutinib were not available and nilotinib and dasatinib alone remained, would be patients with: – diabetes – CV disease – -CV risk factors – -pulmonary disease (compromised respiratory function) – -PAH – -existing pleural effusions There is no single agent that can be described as 'best alternative care', as the choice of therapy is specific to the patients disease status and co-morbidities. This is also stated in previous submissions for first line dasatinib and nilotinib, which have been NICE approved.	
Outcomes	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	We believe these are as needed and have no further comment on outcome measures.	Comment noted. No changes to the scope are needed.

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	ACP-NCRI CML Working Party-RCP-RCPath-BSH	Yes. The probability of being able to come off therapy should also be considered however. This is detailed in the 'Background' section'	Comments noted. No changes to the scope are needed.
Economic analysis	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	We have no major comments on the specification of the economic analysis. Sufficient evidence to assume similar or greater health benefits between the intervention and comparator technologies will be required if a cost-comparison analysis is being considered.	Comments noted. No changes to the scope are needed.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	The cost analysis appears as for previous first line nilotinib or dasatinib. The appropriate time horizon from a clinical perspective would be in the next 6 months.	Comments noted. No changes to the scope are needed.
Equality and Diversity	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	We have no comments regarding equality.	Noted.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	If patients fail TKI therapy, then the only curative approach is with a stem cell transplant (SCT). Patients from non- European ethnic origins are far less likely to have an available matched unrelated donor. By not allowing tolerable treatment to these racial groups, this pushes their therapy towards allogeneic SCT, which is less likely to be available to them. Other potential patient groups that would be affected, are those with pre-existing co-morbidities (as detailed in the comparator section), as these	Comments noted. No changes to the scope are needed. This is acknowledged in the equality impact assessment published with the final scope.

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		conditions may preclude them from receiving 2G-TKI therapy, or their co-morbidities may be potentially aggravated by dasatinib or nilotinib. The evidence is detailed in the Summary of Product Characteristics for dasatinib or nilotinib and on previous first line appraisals for these drugs.	
Other considerations	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	None.	Noted.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	The technology would be very easy to use, as it would be similar to current management of TKI therapy, with no additional clinical requirements. Haematologists have been very familiar with bosutinib after NICE approval in later lines of therapy. The management of patients on bosutinib would follow ELN recommendations in a straightforward fashion. The monitoring and testing would be equivalent to the current practice of all other TKIs with no formal additional tests required. As with the other 2G -TKIs (nilotinib/dasatinib), bosutinib is a more potent TKI and increases the chance of discontinuing life-long TKI therapy. Although this is a concept being evaluated in clinical trials, recent clinical guidelines are providing practical recommendations for this approach. The technology under clinical trial conditions does reflect that of clinical practice. This has now been validated in many independent reviews of standard first line 2nd generation TKI therapy in CML management. The most important outcome is to achieve the expected CCyR with minimal toxicity. Achievement of CCyR is a surrogate marker of survival, and predicts long-term outcome. Additional surrogate markers include achievement of MMR, which is termed a ‘safe haven’ due to its association with a lack of	Comments noted. No changes to the scope are needed.

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		progression. The achievement of MMR and CMR in greater numbers on bosutinib allows for stopping TKI therapy. Most side-effects on bosutinib are low-grade, easily manageable, and importantly reversible. A commonly described side-effect is diarrhoea. This is usually at the onset of therapy, improves with time on bosutinib, and is relatively straight-forward to manage. Patients do not discontinue bosutinib on account of this side-effect. All other TKIs are associated with diarrhoea, but to a lesser frequency than bosutinib. Liver function tests need to be monitored as with all TKIs. Side-effects of therapy as with all TKIs are dose dependent, and can be managed with dose-interruption and adjustment. Bosutinib is the most selective BCR-ABL inhibitor available. All other TKIs have inhibitory activity against other signalling pathways (c-kit, PDGFR) which are thought to be responsible for side-effects. Bosutinib has no effect on either of these pathways. Haematologists are very aware of the bosutinib spectrum of side-effects and their management.	
Innovation	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	None.	Noted.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	Yes. Tailored CML therapy, in line with modern management of CML patients. Access would maintain high standards of clinical practice as in other developed countries.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee. No changes

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		Yes. As detailed before, access to bosutinib may allow some patients to tolerate TKI therapy better, reducing the intervention on other disciplines (cardiology, respiratory in the main). The evidence with regard to side-effects of dasatinib/nilotinib therapy is detailed in the Summary of Product Characteristics for dasatinib or nilotinib and on previous first line appraisals for these drugs.	to the scope are needed.
Questions for consultation	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	None.	Noted.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	Out-standing questions that may not be addressed in the body of the application: Where do you consider bosutinib will fit into the existing NICE pathway for blood and bone marrow cancers? Bosutinib should be equally available for first line CML therapy, as is nilotinib and dasatinib. There is no difference in drug efficacy, only in the side-effect profile. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Additional data would be available from the first line bosutinib study, accepted by JCO and presented at a number of international meetings. Data on stopping TKI is available from the UK DESTINY study, STIM and EURO-SKI studies. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No barriers as stated in the body of the submission due to clinical expertise with the drug in later lines of therapy, and adherence to national and international guidelines.	Comments noted. No changes to the scope are needed.

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Additional comments on the draft scope	Pfizer	No comments.	Noted.
	Bristol-Myers Squibb	None.	Noted.
	ACP-NCRI CML Working Party-RCP-RCPath-BSH	With the approval of first-line bosutinib by NICE, haematologists would be able to improve and more specifically treat their patients according to their Sokal risk score and co-morbidities. Importantly they would not be placing their patients at risk of worsening co-morbidities. Responding CML patients have a survival which is independent of their CML diagnosis, therefore it is essential that irreversible complications on account of TKI therapy are avoided. NHS staff already have experience with bosutinib according to its existing availability for CML therapy. By approving this technology, NICE would only enhance opportunity and reduce the impact on patients with particular co-morbidities as out-lined above. In order for NICE to fully achieve its goal for the pursuit of equality this Appraisal needs to incorporate the use of bosutinib for first line use in CML, and according to its licence.	Comments noted. No changes to the scope are needed.

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

Leukaemia Care
Novartis
Department of Health