National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Dasatinib, nilotinib and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia (including part-review of TA 70)

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	NHS Quality Improvement Scotland	Reasonable. It states the median life expectancy is 15 years - such figures are from the imatinib era.	Comment noted. No actions requested.
	Bristol-Myers Squibb	Accurate and complete	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK Limited	Second paragraph: The course of disease progression given in the draft scope reflects the situation prior to the availability of imatinib. The context of the description of the course of CML should be made clearly in the scope. Novartis request that the second sentence in this paragraph is changed from: "After around 3-5 years about two-thirds of patients experience a transition into the accelerated phase or blast crisis." to: "Prior to the availability of imatinib, after around 3-5 years in chronic phase, about two-thirds of patients experienced a transition into the accelerated phase or blast crisis." Third paragraph: This paragraph should establish the fundamental role of BCR-ABL in CML. This is vital to the development of drugs to effectively treat CML. Novartis request that the following sentence is added to the end of this paragraph: "BCR-ABL is the only known cause of CML." Last paragraph:This sentence does not accurately reflect the current medical opinion on the first-line treatment of chronic phase CML patients. Novartis request that the text in this paragraph is changed from: "Alternative first-line treatment options include hydroxycarbamide, interferon alpha, and allogenic stem cell transplantation. NICE is currently appraising dasatinib and nilotinib for imatinib-intolerant CML. An appraisal of dasatinib, nilotinib and high-dose imatinib for imatinib-resistant CML (part-review of TA70) is also underway." to "In the absence of imatinib and more recently developed second-generation TKIs, alternative first-line treatment options would include hydroxycarbamide (HU), interferon (IFN) alpha, and allogenic stem cell transplantation (SCT). However, in practice and in accordance with expert clinical opinion, HU and IFN-alpha are no longer considered as first-line treatments, except in exceptional circumstances. SCT is associated with significant morbidity and mortality and, therefore is generally not recommended until after imatinib therapy has been used as a first-line treatment. NICE is currently appraising dasatinib and nilotinib for imatinib-intolerant CML. An appraisal of dasatinib, nilotinib and high-dose imatinib for imatinib-resistant CML (part-review of TA70) is also underway."	Comment noted. Text has been changed in response to this and to similar comments received. Comment noted. The sentence 'BCR-ABL is the only known cause of CML'. Has been added to the text. Comment noted. The text 'alternative first-line treatment options include hydroxycarbamide, interferon alpha, and allogenic stem cell transplantation' has been removed from the background section of the scope.

Section	Consultees	Comments	Action
	NHS North Yorkshire & York	No comment	Comment noted. No actions requested.
	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	Whilst not directly relevant to the rest of the scope, the second paragraph of the background is rather out of date and inaccurate. Firstly, 3 separate studies show that around 60% of patients who start treatment with imatinib at standard dosage (400 mg daily) will remain in chronic phase and in complete cytogenetic remission (CCR) for at least 5 years (the long term follow-up of the IRIS trial (O'Brien et al presentation at ASH 2008), local experience at the large CML centre at Imperial (de Lavallade et al 2008) and a population based study in the North-West (Lucas et al 2008)). Secondly, in the current TKI era, accelerated phase is much less clear cut, since most progressing patients may move from seemingly stable chronic phase straight into blast crisis, without any intervening transitional stage. Thirdly, in patients treated since original diagnosis, far less than one-third of patients will transform to blast crisis at 8 years (follow-up beyond this time is not yet available). As a result of these considerations, it is highly likely that the annual death rate attributable to CML is now far less than the 200 per annum quoted in paragraph 4 of the Background, though there are currently no data on this to our knowledge. In fact, it is hard to square this death rate with the statement in the following sentence of the same paragraph, that the median life expectancy is 15 years. There are certainly no data on this, since no newly diagnosed patient received any TKI until mid 2000. The '200 per annum' death rate is likely derived from a pre-TKI era, whereas the median life expectancy of 15 years is from speculative extrapolation of current survival data.	Comment noted. Text has been changed in response to this and to similar comments received. Comment noted. The reference to 200 deaths has been removed from the scope.
The technology/ intervention	NHS Quality Improvement Scotland	Yes	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	Bristol-Myers Squibb	Suggest change the second sentence in this section to: 'These particular TKIs…' instead of 'TKIs…'	Comment noted. Text changed to 'These particular TKIs'.
		Suggest change the last sentence in this section to 'The recommended starting dosage of imatinib is 400mg/day for patients in chronic phase CML. Dose increases from 400 mg to 600 mg or 800 mg in patients with chronic phase disease can be considered if it is appropriate'	Comment noted. Text changed to 'The recommended starting dosage of imatinib is 400mg/day for patients in chronic phase CML'. No reference to dose escalation was thought to be necessary for this appraisal given that we are specifically appraising imatinib at a dose of 400mg/day.
	Novartis Pharmaceuticals UK Limited	The technologies. First paragraph: The TKIs being appraised differ in the specificity for inhibiting BCR-ABL. Novartis request that the following text is inserted after the last sentence of the first paragraph: "Imatinib and nilotinib have a high specificity for the BCR-ABL protein, whilst dasatinib acts on multiple targets."	Comment noted. Added: 'Imatinib and nilotinib have a high specificity for the BCR-ABL protein, whilst dasatinib acts on multiple targets' to text.
		Third paragraph: This paragraph should be updated to reflect recent developments regarding the marketing authorisation for nilotinib. In September 2010, nilotinib received a positive CHMP opinion, with marketing authorisation expected in November/December, 2010.	Comment noted. Text has been changed to reflect marketing authorisations.
	NHS North Yorkshire & York	No comment - valid comparators	Comment noted. No actions requested.

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	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	Yes	Comment noted. No actions requested.
Population	NHS Quality Improvement Scotland	It would be better to consider patients in whom transplant is an option (<60 yrs for example) separately and include transplant as a comparator. This is after all how younger patients were managed pre imatinib. Transplants have potential for huge toxicity and ongoing costs - the new interventions are likely to be more cost effective in these groups.	Comment noted. Transplant was not considered an appropriate comparator for first line treatment in the chronic phase based on responses from the majority of consultees.
	Bristol-Myers Squibb	Appropriate	Comment noted. No actions requested.
	Novartis Pharmaceuticals UK Limited	No comments	Comment noted. No actions requested.
	NHS North Yorkshire & York	No comment	Comment noted. No actions requested.
	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	No issues	Comment noted. No actions requested.

Section	Consultees	Comments	Action
Comparators	NHS Quality Improvement Scotland	Hydroxycarbamide is NOT a viable comparator, This is used very occasionaly in an elderly frail pt or a pt with serious co-morbidities. It should NOT be used. It has no effect on the history of the disease. Allogeneic stem cell transplant HAS to be included.	Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib. Allogeneic stem cell transplant was not considerd an appropriate comparator for first line treatment in the chronic phase.
	Bristol-Myers Squibb	Hydruxycarbamide and interferon alfa are not standard of treatments currently used in the NHS. Neither of them can be described as 'best alternative care'. Imatinib 400mg is the standard of treatment currently used in the UK and has been approved by NICE The comparator should be imatinib 400mg, as stated in the previous draft scope for technology appraisal of dasatinib in 1st line use.	Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib.
	Novartis Pharmaceuticals UK Limited	The comparators in the draft scope do not represent the current standard treatment for first-line treatment of CML, which is imatinib. Expert medical opinion is that since the introduction of imatinib, neither HU nor IFN is used in the first-line treatment of CML, except in exceptional circumstances.	Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib.

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	NHS North Yorkshire & York	Agree Locally stem cell transplantation is considered after failure of imatinib and potentially after dasatinib/nilotinib as 2nd line agents, therefore we would not consider it as an appropriate 1st line comparator for this MTA.	Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib.
	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	Whilst alpha interferon (IFN) is listed as an alternative technology, the IRIS trial (which compared imatinib and IFN) collapsed after 18 months, since imatinib was clearly superior on both efficacy, toxicity (O'Brien et al 2003 and Druker et al 2006; both NEJM) and quality of life (Hahn et al; JCO 2003). Furthermore, although no randomised trial has compared imatinib vs. allogeneic BMT as first line treatment, almost all CML groups would recommend imatinib in preference, since this avoids the procedure-related mortality of at least 25% associated with BMT. This is certainly true in adults, and paediatric colleagues are increasingly taking the same view. Thirdly, we know that the clearance of CML from the marrow (CCR) correlates with a better progression-free survival. Hydroxycarbamide never achieves CCR, whereas at least 70% of patients will do so on imatinib; hydroxycarbamide is therefore obsolete and probably unethical as first line treatment in 2010. Therefore, the only realistic comparator for the 2G TKI is imatinib at 400 mg daily.	Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib.
Outcomes	NHS Quality Improvement Scotland	Yes	Comment noted. No actions requested.
	Bristol-Myers Squibb	Yes	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK Limited	Novartis request that the following outcome measures are included in addition to those already in the draft scope: • Time to progression • Time to, and duration of, MMR and CCyR • Percentage of patients achieving BCR-ABL ratio of equal to or less than 0.01% and 0.0032%	Comment noted. Time to progression has been added to the list of outcomes. It was considered that time to, and duration of, MMR and CCyR would be captured within the response rates outcome. Percentage of patients achieving BCR-ABL ratio of equal to or less than 0.01% and 0.0032% was not included within the list of outcomes as NICE does not specify specific outcomes measures (NICE. Guide to the methods of technology appraisal, 2008)
	NHS North Yorkshire & York	No comment - Agree with all those listed	Comment noted. No actions requested.
	NCRI/RCP/RCR/ACP/JCCO Royal College of Pathologists, BSH and RCP.	Yes	Comment noted. No actions requested.

Section	Consultees	Comments	Action
Economic analysis	NHS Quality Improvement Scotland	I cant see any mention of what the time horizon will be.	Comment noted. In the table in the scope, under economic analysis there is text that says: 'The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared'.
	Bristol-Myers Squibb	No comments	Comment noted. No actions requested.
	Novartis Pharmaceuticals UK Limited	No comments	Comment noted. No actions requested.
	NHS North Yorkshire & York	No comment	Comment noted. No actions requested.

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	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	Our greatest concern for this proposed MTA is regarding its timing, which we believe is at least a year too early. At present, the available clinical data on dasatinib and nilotinib are very limited. For dasatinib, results at 12 months in the DASISION trial (comparing dasatinib vs. imatinib) have been published (Kantarjian et al 2010, NEJM), but 24 month outcome data are unlikely to be presented until ASCO/EHA 2011, in June 2011. There are also non-randomised data of first line dasatinib in about 50 cases from the MD Anderson. For nilotinib, the results at 12 months in the ENESTnd trial (comparing nilotinib vs. imatinib) have been published in the same NEJM edition as DASISION (Saglio et al 2010), and incomplete 18 and 24 month outcome data were presented at ASCO/EHA 2010 and will be completed at ASH 2010. There are also non-randomised data of first line nilotinib in about 73 Italian cases and 50 cases from the MD Anderson. In addition, bosutinib has recently been compared to imatinib in a phase III randomised trial, and it is highly likely that the results will be presented at the American Society of Hematology annual meeting around Dec 5th 2010, albeit with limited follow-up. Therefore, an appraisal during 2011 will be able to consider randomised published data at 12 months for each drug, and additional data at 18 months for dasatinib and 24 months for nilotinib. Although these randomised comparisons currently clearly show that the 2G TKI are superior for efficacy, progression rates and (possibly toxicity), no overall survival data are yet apparent due to the limited follow-up. It would therefore be a more efficient use of resource to delay this appraisal for at least 12 months, until the randomised trial data are more mature.	All three technologies have received their marketing authorisations. NICE aims to issue guidance as close as possible to the time of marketing authorisation.
Equality	NHS Quality Improvement Scotland	None	Comment noted. No actions requested.
	Bristol-Myers Squibb	None	Comment noted. No actions requested.

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	Novartis Pharmaceuticals UK Limited	No comments	Comment noted. No actions requested.
	NHS North Yorkshire & York	No comment	Comment noted. No actions requested.
	NCRI/RCP/RCR/ACP/JCCO Royal College of Pathologists, BSH and RCP.	No issues	Comment noted. No actions requested.
Other considerations	Bristol-Myers Squibb	********** ********** ********** (Commercial in confidence information removed)	Comment noted. All products to be included within the appraisal are administered orally. No changes to the scope made.
	Novartis Pharmaceuticals UK Limited	No comments	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	NHS North Yorkshire & York	Genetic mutations - we note that the presence of genetic mutations have been reported to be associated with resistance to one or more of the drugs included in this MTA e.g.T315I mutation. On that basis we would ask for consideration of the evidence and the costs (if additional to routine testing) this may have on the population or subgroup, and thus how this may impact on the cost analysis. Would appreciate consideration of evidence and rationale for switching between agents after failure of the initial drug (on grounds of adverse effects or failure to respond to treatment), acknowledging this may be considered outwith the scope of this MTA but a purtinent question	Comment noted. In the other considerations section of the scope we have included the text: 'If evidence allows, the appraisal will consider subgroups based on people with and without genetic mutations'. Comment noted. This appraisal will consider first line treatment only. Therefore switching will not be considered. No changes to the scope have been made.
	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	No issues	Comment noted. No actions requested.

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Questions for consultation	NHS Quality Improvement Scotland	Yes. Imatinib is now standard of care worldwide - it has transformed CML into a disease managed chronically sucgh as diabetes, rather than a universally fatal cancer. Life expectancy will likely approach normal for most patients. For the most part patients feel well on these drugs and return to a productive working life. This has to be taken into account - historically many patients on interferon or post BMT remained unwell and could not work. For patients having had a good response to these drugs, hospital visits can be reduced to 6 monthly (as compared with every few weeks in the days of interferon, or twice weekly post transplant). Not sure I fully understand this question. I presume recent first line data from Nilotinib / Dasatinib will be considered, as well as long term follow up from the IRIS trial. Good transplant outcome data is available from EBMT. It would be unwise not to take into account the European ELN Guidelines on CML, 2009. Presumably robust economic models will be submitted.	Comments noted. No actions requested.
	Bristol-Myers Squibb	No comments	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK Limited	*Do you consider the technology 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)?* Compared with imatinib, nilotinib has a greater binding affinity to, and greater inhibition of, BCR-ABL. It is considered that this may further delay or prevent reactivation of BCR-ABL, thereby reducing the likelihood of resistance and ultimately, disease progression[1]. Twelve and eighteen month follow-up data from the pivotal registration trial for nilotinib as a first-line treatment in CML (ENESTnd[2]) has demonstrated that nilotinib has significantly improved efficacy compared with imatinib. *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* In the ENESTnd trial, when compared with the current standard of care (imatinib 400mg OD), nilotinib (300 mg BD) doubled the rate of major molecular response (MMR) at 12 months. In addition, nilotinib nearly triples the probability of a patient having their CML reduced to undetectable levels (i.e. achieving Complete Molecular Response (CMR)) during the first 18 months of treatment.	Comment noted. No actions requested. Comment noted. No actions requested.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK Limited (cont)	*Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Nilotinib has been compared with the current standard of care, imatinib, in a large phase III randomised trial, ENESTnd[2], using MMR at 12 months as the primary endpoint. This trial showed that nilotinib 300mg BD doubles the proportion of patients reaching MMR compared with imatinib (44% vs 22%, p<0.0001, Cochran–Mantel–Haenszel test stratified by Sokal risk group). This increase in the proportion of patients achieving MMR with nilotinib was seen across all levels of baseline risk. Those patients randomised to nilotinib also tended to achieve MMR more rapidly than those on imatinib. ENESTnd demonstrated that < 1% of patients treated with nilotinib progressed to advanced phases of CML. The trial also showed that nilotinib is generally well tolerated. This trial formed the basis of the regulatory submission to the EMA for nilotinib. These efficacy and safety results are supported by an independent phase II study on the proposed licensed dose of nilotinib by the All Ireland Cooperative Oncology Research Group (ICORG)[3], which demonstrates that chronic phase CML patients on nilotinib rapidly achieve MMR and CCyR, with low rates of progression to advanced stages and few adverse events. Nilotinib for chronic phase CML has also been examined in two other phase II studies, although not at the proposed licensed dose (trials by Gruppo Italiano Malattie EMatologiche dell'Adulto[4] and the MD Anderson Cancer Center[5]).	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK Limited (cont)	*Has the population been defined appropriately?* Yes *Have the most appropriate comparators for dasatinib, nilotinib and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia been included in the scope?* NICE have included comparators in the draft scope of nilotinib that do not reflect current clinical practice. The most appropriate comparator for nilotinib is the current standard of care, imatinib. *Are the comparators listed routinely used in clinical practice?* No. HU and IFN are no longer considered as a first-line treatment option for chronic phase CML, other than in exceptional cases. *Should stem cell transplantation be included as a comparator in the scope?* In the absence of TKIs, SCT is a valid comparator as a first-line treatment, although this is only suitable for a subset of CML patients. *Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?* No *Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?* Not to our knowledge.	Comment noted. No actions requested. Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib. Stem cell transplant was not considerd an appropriate comparator for first line treatment in the chronic phase. Comment noted. No actions requested. Comment noted. No actions requested.

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	NHS North Yorkshire & York	At present we do not consider the technology to be innovative - the use of TKI inhibitors for the treatment of CML reflects clinical practive locally over recent years with imatinib followed by a newer generation agent e.g. dasatinib or nilotinib. At present, I am unclear of the significant clinical advantages of using dasatinib or nilotinib as alternative 1st line agents, costs will be dependent on dose and local procurement arrangements. Of particular importantance will be the anticipated cost savings for Glivec (imatinib) due to follow its patent expiry which is anticipated 2016.	Comment noted. No actions requested.
	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	Yes. Though very early, currently avalable data from randomised trails for each drug (dasatinib and nilotinib) show better achievement of surrogate survival endpoints (CCR and MMR). Even more important, the rates of progression are lower with each drug (statistically significant with nilotinib, not with dasatinib). These data do however need to mature, since it is is theoretically possible (though unlikely) that patients on standard imatinib may 'catch up' with those on the newer drugs at later follow up. We have concerns that this appraisal may be too early for this effect to be detected. Can it be delayed until 2012 or later?	All three technologies have received their marketing authorisations. NICE aims to issue guidance as close as possible to the time of marketing authorisation.
Additional comments on the draft	Bristol-Myers Squibb	No comments	Comment noted. No actions requested.

Section	Consultees	Comments	Action
scope.	Novartis Pharmaceuticals UK Limited	None References: 1. Kantarjan HM, Hochhaus A, le Coutre P et al. Nilotinib is highly active and safe in patients with chronic phase chronic myelogenous leukaemia (CML-CP) with imatinib resistance or intolerance. Blood (ASH Annual meeting abstracts) Nov 2007;110:735. Oral presentation 2. Saglio G et al, Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia NEJM 2010 Jun 17;362(24):2251-2259 3. O'Dwyer ME et al. Nilotinib 300 mg twice daily is effective and well tolerated as first line treatment of Ph-Positive chronic myeloid leukemia in chronic phase: preliminary results of the ICORG 0802 phase 2 study. Blood (ASH) Annual Meeting Abstracts 2009;114:Abstract 3294 [ICORG]. 4. Rosti G et al. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. Blood 2009;114:4933-4938. 5. Cortes J. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol 2010;28:392-397.	Comment noted. No actions requested.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR /ACP/JCCO Royal College of Pathologists, BSH and RCP.	The wording of the 'comparators' box on p3 may need revision. This states that 'the interventions (i.e. the 2G TKI and imatinib) will be compared with each other, in line with their marketing authorisations'. Neither dasatinib nor nilotinib (nor bosutinib) currently have a UK marketing authorisation for first line use, though EMEA approval is granted and presumably will soon be applied to the UK. It would be helpful to clarify that first line comparison is indeed what is intended. Furthermore, several studies have compared imatinib 400mg with higher doses either at 800 mg daily (TOPS, German GEIST/CML 4, non-randomised MD Anderson data) or at 600 mg daily (French ESPRIT). Is it intended to include these comparisons of imatinib dosage in the appraisal? As above, it is unrealistic to compare with hydroxycarbamide or interferon alpha (or BMT) since the only comparator that is actually NICE approved is imatinib 400 mg daily.	Comment noted. Based on this and other related comments, relevant comparators for this appraisal are considered to be dasatinib, nilotinib and standard-dose imatinib (400md/day only). The appraisal is for first-line treatment of chronic CML.

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

Medicines and Healthcare products Regulatory Agency
Public Health Wales NHS Trust
Department of Health
Welsh Assembly Government
Foundation for Liver Research
Royal College of Nursing
Macmillan Cancer Support