National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic 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
Appropriateness	*It is important that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would this topic be appropriate for a NICE appraisal?*		
	ARIAD Pharmaceuticals /Incyte Corporation	Appraisal of ponatinib (Iclusig) is both appropriate and timely, as this breakthrough therapy addresses important clinical needs in patients with particularly difficult-to-treat forms of chronic myeloid leukaemia (CML) and Ph+ acute lymphoblastic leukaemia (Ph+ ALL), two progressive and ultimately fatal cancers. This appraisal should be accorded a high priority, as in the absence of effective alternative pharmacologic treatment options the indicated patient population is at high risk for progression and death.	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	Leukaemia CARE	Leukaemia CARE consider it appropriate to refer this topic to NICE for appraisal. Three of the five TKI's developed for the treatment of CML are currently funded via the Cancer Drugs Fund. They are currently being reviewed to decide if they shall receive routine funding in the future (due to reform to the CDF). As such, the future of access to these drugs (dasatinib, bosutinib and ponatinib) for patients in England is now unclear. Similarly, ponatinib for the treatment of ALL (for patient who have the T315i	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.

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		mutation), currently funded by the CDF in the interium, is also being reviewed. Due to the limited number of treatment options available to ALL patients in this setting, it is imperative that ponatinib remains accessible (following the CDF reform).	
	Pfizer	We consider it appropriate for this topic to be referred to NICE for appraisal.	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	NCRI-RCP-ACP	Yes. All other TKIs have been NICE appraised. Although the population is smaller for ponatinib, it remains important as the patients potentially receiving ponatinib are those with the greatest clinical need. It is appropriate to review this for Ph+ ALL as well but the 2 conditions are completely different and the indications are completely different	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	Bristol-Myers Squibb Pharmaceuticals	We agree that ponatinib is an appropriate and important topic for NICE appraisal.	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	Yes it would be appropriate to refer this topic to NICE for appraisal because: (i) There is a very small group of patients for whom ponatinib remains the only treatment offering the possibility of securing clinical efficacy, assuming: (a) stem cell transplantation (SCT) is considered not to be either an approrpriate and/or feasible option (b) they have either experienced failure following bosutinib treatment or for whom bosutinib treatment is not considered appropriate. For this group of patients, ponatinib answers an unmet need. (ii) For an even smaller group of patients exhibiting the T315i mutation, the only currently available tyrosine kinase inhibitor (TKI) treatment known to	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.

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		be capable of being clinically effective is ponatinib. In these circumstances ponatinib also answers an unmet need (iii) There is a clinical evidence base supporting a proposition that ponatinib treatment could prove an effective treatment for a signficant number of, although not all, patients exhibiting resistance following nilotinib and/or dasatinib treatment.	
	NHS England	Yes – there is a clear desire from clinicians to access this treatment in both the CDF approved and wider licensed indications	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	Royal College of Pathologists	Yes. At present there are patients who could benefit from ponatinib who do not have access to the drug	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*		
	ARIAD Pharmaceuticals /Incyte Corporation	The current wording of the draft remit appropriately reflects the use of ponatinib according to its marketing authorisation.	Comment noted. No action required.
	Leukaemia CARE	The draft remit is for the purpose "to appraise the clinical and cost effectiveness of ponatinib within its licensed indication for treating chronic myeloid leukaemia". We feel that is should be expanded to fully state the license indication of ponatinib to ensure clarity of what the drug is being appraised for. I.e. • chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are	Comment noted. The full wording of the marketing authorisation in the UK is specified in 'the technology' paragraph and in the 'population' section of

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		intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315i mutation	the table in the scope. No action required.
	Pfizer	We consider the wording of the remit of this appraisal to be appropriate.	Comment noted. No action required.
	NCRI-RCP-ACP	Yes	Comment noted. No action required.
	Bristol-Myers Squibb Pharmaceuticals	We have no comments regarding the remit of the NICE appraisal.	Comment noted. No action required.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	Yes the wording of the 'Draft remit/appraisal objective' does so.	Comment noted. No action required.
	NHS England	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Timing Issues	*What is the relative urgency of this appraisal to the NHS?*		
	ARIAD Pharmaceuticals /Incyte Corporation	The need for this appraisal is of the utmost urgency, as there has already been nearly a 3-year delay between the marketing authorisation of ponatinib and the current draft scope from NICE. Since the launch of ponatinib, no formal assessment has taken place in England. NICE did conduct a scoping process in 2013 but chose not to appraise ponatinib as the patient population was considered to be too small. However, another agent with a similarly sized patient population – bosutinib – was appraised by NICE nonetheless. This has led to inequity of access to ponatinib across the UK, as ponatinib has been formally evaluated in Scotland and Wales and is available there, but patients in England who fall within the EC label, but do not have the T315I mutation, are unable to access the product. This is because eligibility to receive ponatinib in England through the Cancer Drugs Fund (CDF) is	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.

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		currently restricted to the subgroup of patients with documented T315I mutation, thereby excluding a substantial proportion of the indicated population. The magnitude of this lack of coverage is indicated by the fact that 74% of the CML subjects in PACE (the pivotal ponatinib study) did not have the T315I mutation. The inequity of access will remain the situation until a formal assessment is conducted in England and we believe this assessment should be a priority given the significant delay to date. Considering the progressive nature of late-line leukaemia in the absence of effective treatment, any further delay in appraisal will place patient lives in jeopardy.	
	Leukaemia CARE	We feel that there is urgency to this appraisal because although ponatinib is currently funded via the CDF for CML and ALL patients, access is restricted to patients who have the T315i mutation. Patients in England who do not meet this criteria are currently unable to access ponatinib. Ponatinib, as an effective, innovative TKI, should be available to all CML and ALL patients in England for its full licensed indication. We also feel that it is imperative that there is access for patients in both settings via the Cancer Drugs Fund across the full indication (rather than just for T315i patients) whilst the appraisal is ongoing. As far as we are aware, ponatinib is the only drug in the CDF 'group 3' that is not being funded across its full indication whilst the appraisal takes place. It is inequitable that there is no access for these patients in England, whilst it is routinely commissioned in Scotland and Wales. Leukaemia CARE would agree that there is urgency to this appraisal due to the currently limited number of treatment options for relapsed or refractory CML and ALL patients and the clinical efficacy of the drug for patients in both settings. Finally, there is currently no NICE treatment pathway for patients with ALL. As such, there is a distinct unmet need for additional, effective second line	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.

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		treatments in this already hard-to-treat haematological area	
	Pfizer	We consider the timing of appraisal to be appropriate	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	Very urgent. I. NICE convened a scoping workshop in November 2013 following which a referral was not sought because the Institute was 'of the opinion than an appraisal of ponatinib' for CML treatment was 'not appropriate, noting that the population size was very small'. II. The revisions to Guide to the Methods of TA (in particular section 2.3.3) effective from 1st April 2016 indicates that population size is no longer an issue that would be pertinent in a decision as to whether NICE should seek a referral.	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	NCRI-RCP-ACP	Urgent as options limited for patients resistant to other TKIs – imatinib, nilotinib	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	Bristol-Myers Squibb Pharmaceuticals	We have no comments regarding the timing of this appraisal.	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
	NHS England	There is clear clinical demand for this product in its non-CDF approved indication which has now been licensed for some time. This should be balanced against the relatively small patient numbers eligible for treatment	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology

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			appraisal work programme.
	Royal College of Pathologists	Urgent – there are patients in need of ponatinib at present, who will have to be considered for allogeneic stem cell transplant unless they can gain access to the drug	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.
Additional comments on the draft remit	The Chronic Myeloid Leukaemia Support Group (CMLSg)	* Ponatinib is a Group 3 member of the CDF Rapid Reconsideration cohort with Group 3 members accounting for 12 (or 30%+) of the 37 drug: indications pairs in the three groups that make up the cohort. * The most recent information about the timeline for processing the appraisals for Group 3 members indicates it is not fixed but rather NICE '...would endeavour to conclude the appraisals by the end of 2017' (NICE Board paper March 2016. Item 6, section 5). * It would be perverse, if not inequitable, if cancer drugs defined as 'new' were to emerge from the standard NICE TA process with recommendations, particularly those that would qualify for their use within the CDF, before Group 3 member appraisals have been completed. *It should be remembered that Group 3 appraisals are not restricted to drug: indication pairs that are current CDF list members but are based on the question the appraisal seeks to answer. The latter is not necessarily the same as the former. * This is applicable for ponatinib which has only the T315i indication in the current CDF national list yet includes indications other than this in the draft scope.	Comments noted. An appraisal of ponatinib has been scheduled into NICE's technology appraisal work programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background	*Consider the accuracy and completeness of this information.*		

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information	ARIAD Pharmaceuticals /Incyte Corporation	CML: The Background section as currently written is generally accurate. For the sake of completeness, we suggest specifying in paragraph 5 that "People who receive treatment with a first- or second-generation tyrosine kinase inhibitor … may develop drug resistance …" since the third-generation (3G) tyrosine kinase inhibitor (TKI) ponatinib has been demonstrated to suppress the emergence of mutations conferring resistance to the first-generation TKI imatinib and the second-generation (2G) TKIs dasatinib, nilotinib, and bosutinib. In addition, we recommend editing paragraph 6 to read, "Other treatment options in clinical practice can include allogeneic [note spelling correction] stem cell transplantation (depending on the availability of a suitable donor and the eligibility of the patient) …" since only a small percentage of CML patients are suitable candidates for this procedure. Based on data from the British Society of Blood and Marrow Transplantation, the UK Haematological Malignancy Research Network and national population statistics, we estimate that approximately 1 in 12 CML patients in England receives allogeneic stem cell transplantation (allo-STC). Ph+ALL The Background section as currently written is generally accurate. However, stem cell transplantation is considered after induction if the patient achieves a CR and is fit for transplant. In relapsed disease a second transplant may be considered. In addition, for the sake of completeness, we suggest specifying at the end of paragraph one that "For patients with Philadelphia-chromosome-positive ALL, tyrosine kinase inhibitor therapy with imatinib or dasatinib (for imatinib-resistant disease) is considered to be standard of care by NCCN and ESMO clinical guidelines." Accordingly, we suggest removing the phrase "may also be included as a treatment option."	Comments noted. The background section of the scope has been amended. Comments noted. The background section of the scope has been amended.
	Leukaemia CARE	The background information indicates that there are approximately 600 – 800 people diagnosed with CML in England and Wales. We feel it is necessary to	Comments noted. The background section of

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		give a more specific figure than this. As per the CRUK stats for CML incidence in 2013, there were 657 people diagnosed in England and Wales.	the scope has been amended accordingly.
	Pfizer	• Bosutinib should be listed as an alternative tyrosine-kinase inhibitor (TKIs) that patients may receive for the treatment of their disease in the following statement (page 2 of 6): "People who receive treatment with a tyrosine kinase inhibitor (such as imatinib, nilotinib or dasatinib) may develop drug resistance through a number of mechanisms, one of which is the T315I mutation that interferes with the inhibition of tyrosine kinase." • Please note typo on page 2: "allogenic stem cell transplantation" should be read "allogeneic stem cell transplantation"	Comments noted. The background section of the scope has been amended accordingly.
	NCRI-RCP-ACP	In paragraph 1 of the background, to clarify: In the current climate of TKI therapy, only a minority of patients progress to accelerated or blastic phase ~5%) and a small number present in accelerated or blast phase (10-15%). Final paragraph: Other treatment options in clinical practice include interferon alpha. Re ALL it states TKI 'may' be added to therapy. In fact TKI are international standard of care so this needs to be amended. TKI are not optional in the therapy of Ph+ ALL. Allogeneic bone marrow transplant is SOC for Ph+ ALL in CR1 whereas the info mentions more about using chemo and maintenance; this is not really correct. Clofarabine is mentioned; it is not relevant to this situation.	Comments noted. The background section of the scope relating to CML has been amended. Comments noted. The background section of the scope has been amended
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	We are satisfied with the content of the 'Background' section.	Comment noted. No action required.

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	Bristol-Myers Squibb Pharmaceuticals	All background information appeared accurate on our review.	Comment noted. No action required.
	NHS England	This information is accurate	Comment noted. No action required.
	Royal College of Pathologists	It is a reasonable summary of the current situation. It does not include any published results of efficacy or tolerability and presumably this is expected within the detailed appraisal	Comment noted. The efficacy and tolerability of ponatinib will be considered as part of the appraisal. No action required.
The technology/ intervention	*Is the description of the technology or technologies accurate?*		
	ARIAD Pharmaceuticals /Incyte Corporation	The Technology section as currently written is generally accurate. For the sake of completeness, we suggest adding the following text before the last sentence of paragraph 1: "Ponatinib inhibits all native (unmutated) and mutated BCR-ABL variants, including the T315I mutation."	Comment noted. This section is intended to briefly describe the general mechanism of action. No action required.
	Leukaemia CARE	The genetic mutation, in this context, is T315i – the last sentence states "T3151".	Comment noted. The scope has been amended accordingly.
	Pfizer	No comments.	Comment noted. No action required.
	NCRI-RCP-ACP	Yes.	Comment noted. No action required.
	Bristol-Myers Squibb Pharmaceuticals	Yes.	Comment noted. No action required.
	The Chronic Myeloid Leukaemia	In our opinion in addition to describing ponatinib as an oral medication 'The technolgy' section should also extend the sentence that describes its administration to include the features listed below which we are aware	Comment noted. This section is intended to briefly describe the

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	Suport Group (CMLSg)	patients attach significant value to: (a) A situation not applicable for all TKI treatments for CML: (i) Ponatinib is a once per day treatment (ii) Ponatinib requires no pre adminstration fasting (b) TKI treatment, unlike more traditional chemotherapy agents, is: (i) Administered at home (ii) For the overwhelming majority of patients treatment is for life (rather than cyclical with a limit on the number of cycles able to be tolerated).	general mechanism of action. Other features of ponatinib will be considered in more detail as part of the appraisal.
	NHS England	The information is accurate	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*		
	ARIAD Pharmaceuticals /Incyte Corporation	The Population section correctly defines the target population, given the current NICE recommendations for other TKI therapy. We advise against considering subgroups within the target population separately, as this approach underlies the current inequity in CDF access to ponatinib between patients with the T315I mutation and those who fall within the indication but do not have this mutation. High response rates to ponatinib have been demonstrated in PACE regardless of mutation status. In particular, multivariate analyses determined that T315I was not a significant predictor of response, and that confounding factors (especially higher dose intensity and younger age) explain the different response rates between patients with or without the T315I mutation.	Comment noted. No action required.
	Leukaemia CARE	We feel that the population is defined appropriately as, in order to keep in line with availability of ponatinib in Scotland and Wales, the TKI should be available to all CML and ALL patients who require it. We would currently consider there to be a “treatment vacuum” in England for patients (without T315i mutation) who have not been treated successfully with any of the other appropriate TKI’s.	Comment noted. The population wording is consistent with the wording of the marketing authorisation in the UK for ponatinib. No action required.
	Pfizer	Pfizer suggests that the subgroup of patients with the T315I mutation should	Comments noted.

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		be considered as a separate subpopulation, as they have different possible pathways (noted below in the comparators section) and subsequent management. In addition, as section 4.1 of the Summary of Product Characteristics for ponatinib specifies that an assessment of cardiovascular status prior to start of therapy may be required, this sub-population may need to be considered separately (1).	Ponatinib has a marketing authorisation in the UK for the treatment of CML and ALL irrespective of mutational status. Due to the small size of the population it is considered it may be impractical to conduct a subgroup analysis according to cardiovascular status. No action required.
	NCRI-RCP-ACP	Yes for CML For Ph+ ALL – We are concerned that resistance to a particular drug dasatinib is mentioned as the correct population when dasatininib is (as mentioned early in the document) NOT actually available. It's a logical fallacy to make receiving this drug contingent upon receipt of an unavailable agent.	Comment noted. The population wording is consistent with the wording of the marketing authorisation in the UK for ponatinib. No action required.
	Bristol-Myers Squibb Pharmaceuticals	Regarding the treatment of CML: We note the population in the Draft Scope is a variation on the population wording within the ponatinib licensed indication (see below). We assume this is due to access arrangements around alternative BCR-ABL tyrosine kinase inhibitors, namely imatinib, nilotinib, dasatinib and bosutinib. Under current access arrangements, we agree that population as specified is appropriate; however we note that dasatinib is currently being re-appraised by NICE in line with previous appraisals TA251 and TA241. As the manufacturer of dasatinib, we are committed to ensuring that it will be recommended by NICE in the coming months; we therefore suggest the	Comments noted. The wording of the population in the scope has been amended to be consistent with the wording of the marketing authorisation in the UK for ponatinib.

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		population wording for this appraisal be broadened to anticipate and allow for change in access arrangements for dasatinib. This changed wording would be in line with the ponatinib CML indication as follows: Adults with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia, whose disease is resistant to dasatinib or nilotinib (or dasatinib if they have received it because of intolerance to nilotinib), who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation. Amending the population in this manner would be in line with available evidence from clinical trials. It would also be beneficial to the NICE Appraisal Committee, as should dasatinib be successful, there would be no confusion in the requirements for access to ponatinib; however, the Appraisal Committee would still retain the option to provide a recommendation in a subgroup of the total population should it be necessary. Regarding ALL: We would like to flag that dasatinib was delisted from the CDF for the treatment of ALL in November 2015.	Comment noted. The paragraph on 'current treatment for ALL' acknowledges that dasatinib was available through the Cancer Drugs Fund until November 2015. No action required.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	(i) The manner in which the population is defined in the draft scope recognizes various sub populations. For example the existence of three disease phase sub populations and a sub population defined by the presence of the T315i mutation. (ii) We aspire to a definition of the population that reflects the current clinical	Comments noted. No action required.

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		consensus across Europe and is formally set out in 'European LeukaemiaNet recommendations for the management of chronic myeloid leukaemia:2013' (Baccarani M et al Blood 2o13 Aug 8;122(6): 872 -874). This would include ponatinib as a 3rd line treatment after failure to respond to, or intolerance of, two TKIs where one TKI might have been bosutinib. That said, our view is that if ponatinib were to be available in England in any treatment line other than first in any disease phase (ie within its licensed indications), the 4th line chronic phase patient population would contain the majority of patients. The 4th line population size would also outnumber that of the T315i sub group but would still remain very small compared to 1st or 2nd line sub populations as would the overall ponatinib patient population size.	
	NHS England	See questions for consultation	Comments noted. No action required.
	Royal College of Pathologists	I have one major concern regarding the remit. The population for CML is defined as 'Adults with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia, whose disease is resistant to nilotinib (or dasatinib if they have received it because of intolerance to nilotinib), who are intolerant to nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation'. This is not the licence held by ponatinib. The insertion of the phrase regarding dasatinib only if it has been given for intolerance to nilotinib is a feature of the current medically unjustifiable restriction on the use of dasatinib. The decision to use dasatinib in this way was related to cost. There is no difference in the efficacy of dastainib and nilotinib and in certain situations (specific tyrosine kinase domain mutations) dasatinib is indicated over nilotinib. If the manufacturers of dasatinib were to reduce the cost there would be no reason to refuse dasatinib to imatinib or nilotinib resistant patients. It is entirely possible that this will happen. In addition many UK patients received dasatinib first line in the context of the national phase III study. Should any of these require ponatinib, they would be refused because of the wording for the CML population. I believe it would be much better to assess ponatinib along the	Comments noted. The wording of the population in the scope has been amended to be consistent with the wording of the marketing authorisation in the UK for ponatinib.

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		lines of its license, because this will avoid the creation of UK and time-specific restrictions that will necessitate further review when access to dasatinib and bosutinib change	
Comparators	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*		
	ARIAD Pharmaceuticals /Incyte Corporation	CML: We agree that allogeneic stem cell transplantation (allo-STC) and best supportive care are relevant comparators, but we do not consider bosutinib to be an appropriate comparator. In its technology appraisal guidance 299, NICE did not recommend bosutinib for CML treatment, and we do not consider it appropriate for ponatinib to be compared to treatments that NICE has explicitly rejected from recommended treatment pathways. Additionally, bosutinib is subject to an ongoing CDF transition review for its full indication, and comparators listed in the final scope include allo-STC, hydroxycarbamide, interferon-alfa, and best supportive care. Despite the fact that ponatinib has had a marketing authorization in the UK since 2013 and is available through the CDF, the transition review for bosutinib has not included ponatinib as a comparator. This supports our contention that these two TKIs are not appropriate comparators for each other—indeed it would be difficult to justify not including ponatinib as a comparator in the bosutinib review if bosutinib is to be included as a comparator in the ponatinib assessment of relevance here. The CML indications for ponatinib and bosutinib differ substantially, such that use of bosutinib in some patient groups for which ponatinib is indicated could represent off-label use, which should not be incorporated into this assessment. Specifically, whereas the ponatinib label notes that ponatinib is recommended for patients with the T315I mutation, the bosutinib label explains that bosutinib has limited activity against this mutation, and therefore clinical activity in patients with the T315I mutation is not expected. More importantly, the bosutinib indication restricts use to patients who have been	Comments noted. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).

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		previously treated with ≥1 TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, which is not readily comparable with the detailed wording regarding resistance and intolerance in the ponatinib label. Given all of the reasons listed above, we believe that bosutinib should not be considered a comparator for ponatinib.	As bosutinib is available through the Cancer Drugs Fund for some people with CML (at the time the scope was written), it is considered to be established clinical practice in the NHS. The wording in background section and the comparator section of the table in the scope acknowledges that it is currently undergoing NICE appraisal. No action required.
		Ph+ALL: We agree that chemotherapy followed by allogeneic stem cell transplantation (allo-STC) or best supportive care (BSC) are relevant comparators. In contrast to the outcome in children with ALL, most adults who develop this condition do not become long-term survivors. Outcomes have been poor, particularly if treatment involves only chemotherapy and not allo-SCT. Imatinib and dasatinib have demonstrated significant antileukaemic activity in patients with refractory or relapsed Ph+ ALL, including patients who had prior transplantation. However, relapse occurs quickly, and survival remains extremely limited. We note that dasatinib is no longer available for Ph+ALL patients in the UK. Importantly, neither nilotinib nor bosutinib are licensed in this indication. As patients eligible for ponatinib under the licensed indication must have	Comments noted. The comparators section of the table in the scope has been amended to remove allogeneic stem cell transplantation as a comparator for ALL. As suggested, ponatinib may support the remission to enable a transplant, therefore it is not considered a comparator. No further

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		failed dasatinib, and imatinib must be clinically inappropriate, or they must have the T315I mutation, the only currently available alternative therapy to ponatinib is allo-SCT, which remains the treatment of choice for eligible adult patients with Ph+ ALL who have a matched sibling or unrelated donor. In general, allo-SCT in these cases requires achievement of a second complete remission with a rescue regimen that must be effective and with as little associated toxicity as possible. Ponatinib can be instrumental in achieving this second complete remission, thus allowing patients to undergo the transplant procedure. Finally, in patients for whom allo-SCT is not suitable, BSC or enrolment in clinical trials could be alternatives. Taking into account these factors, we suggest including as comparators allo-SCT (versus ponatinib followed by SCT), and in patients unsuitable for SCT, we suggest BSC (versus ponatinib, followed by BSC upon ponatinib discontinuation).	action required.
	Leukaemia CARE	Although bosutinib is currently funded on the CDF for chronic phase CML patients, it is under review as per the CDF transition. Following the ongoing review, the initial decision is that it will continue to be funded via NHS England, although the future access to bosutinib as a line of treatment for CML is unclear until the decision is confirmed. There is the possibility that at the end of the transition process, it will no longer be accessible to patients in this setting. We would also argue that although a stem cell transplant is probably the only remaining treatment option for both CML and ALL patients with T315i (should ponatinib be unavailable to them). It should also be acknowledged that given the median age of a CML patient and that of the second peak incidence of ALL (patients being over 60) and the potential associated comorbidities, a SCT may not always be considered an appropriate treatment option. There are a number of complexities associated with a SCT (locating a donor, the associated risks, the variable patient outcomes). This compares to the alternative of ponatinib, which is an effective, innovative oral tablet.	Comments noted. No action required.

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		As “best supportive care” is not an active treatment (i.e. it does not specifically target the leukaemic cells) and is mainly a way of managing the CML symptoms, we would not consider it to be an appropriate treatment option for CML patients. However, in the absence of ponatinib, once patients have exhausted alternative TKI options then if they are unsuitable for SCT, best supportive care may be their only (available) option. We would consider this to be a significant step backwards. We would again like to highlight there is no agreed standard of care for patients with acute lymphoblastic leukaemia (relapsed/refractory) and the best treatment option will often depend upon each patient’s individual situation. As such, an increase in availability of effective treatment options for patients would be welcome progress.	Comments noted. No action required.
	Pfizer	CML The comparators of relevance are different depending on the populations considered: 1. Adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; a. Bosutinib - Subject to the decision of the ongoing NICE CDF transition review (ID1004) b. Best supportive care (including but not limited to hydroxycarbamide). 2. Adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia who have the T315I mutation’. a. Best supportive care (including but not limited to hydroxycarbamide). b. Allogeneic stem cell transplantation (with or without chemotherapy depending on the phase of the disease)	Comments noted. No action required.
	NCRI-RCP-ACP	Agree with comparators which are currently NICE approved. This should also include interferon alpha. Allogeneic stem cell transplantation should include sibling, unrelated donor, cord blood and haplo-identical stem cell transplants.	Comment noted. When selecting the most appropriate

Section	Consultee/ Commentator	Comments [sic]	Action
		For Ph+ ALL transplant is NOT a comparator, it is standard of care. Appropriate compactors would be clinical management without pona and this field is rapidly changing as blinatumomab and (soon) inotuzumab may also be available for that indication	comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013). Interferon alpha has now been included as a comparator in the scope for CML. The term 'Allogeneic stem cell transplantation' has

Section	Consultee/ Commentator	Comments [sic]	Action
			been kept broad so that it can include any of the following: sibling, unrelated donor, cord blood and haplo-identical stem cell transplants. Blinatumomab and inotuzumab are not considered as comparators as neither are established clinical practice in the NHS. Blinatumomab and inotuzumab have not yet received their respective marketing authorisations and are not available through the Cancer Drugs Fund.
	Bristol-Myers Squibb Pharmaceuticals	Regarding the treatment of CML: We note the absence of dasatinib as a comparator and believe this needs to be added, irrespective of whether the suggested change to the population above is adopted. Under current access arrangements, dasatinib has been available via the CDF to a group of patients which aligns with the below population subset from the proposed scope: "[patients] who are intolerant to nilotinib and for whom subsequent treatment	Comment noted. Dasatinib and nilotinib are not considered to be comparators as the wording of the population in the scope specifies that the CML is resistant to dasatinib or nilotinib, or that the person is intolerant to

Section	Consultee/ Commentator	Comments [sic]	Action
		with imatinib is not clinically appropriate" Further, should dasatinib be recommended in the course of its ongoing NICE re-appraisal, it will be available as a first line or second line treatment option in line with current clinical practice guidance, and in line with the comparator treatments specified by clinical experts during the previous Ponatinib scoping workshop, further emphasising the need to include it here as a comparator. We note that if dasatinib is used first line, nilotinib may be a treatment option in the second line setting and may therefore also be a relevant comparator. To ensure the decision problem specified for this appraisal is of most relevance to UK clinical practice, dasatinib and potentially nilotinib should be considered as comparators. Regarding ALL: We have no comments on the comparators specified.	dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate. No action required. Comment noted. No action required.
	The Chronic Myeloid Leukaemia Support Group (CMLSg)	Bosutinib: I. There have been six Decision Summaries with a sole focus on bosutinib published by the NHS England CDF Panel between May 2013 and September 2015 with each Summary subsequent to the first reducing the number of drug:indication pairings for which reimbursement has been made available. II. Bosutinib is currently only available for patients in Chronic Phase disease and only to those who are significantly (Grade 3 or 4) intolerant of dasatinib or nilotinib. III. If drugs that are only available through the CDF are judged to be 'standard treatment(s) currently used in the NHS' then we would argue all bosutinib drug:indication pairings reimbursed via the CDF should be included as comparators even if they have subsequently been delisted. IV. Our reasoning is that section 6.11 (and elsewhere) of the Standard	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Operating Procedures for the CDF 2015/16 permits any patient reimbursed through the CDF to continue to be treated even if the pairing they fall within has been removed from the list. In that sense their treatment remains one that is 'currently used in the NHS'. V. For the avoidance of doubt, we assume that a treatment that is 'standard' (ie available through a recognised route to access, of which the CDF is one variant) is not necessarily one that is 'routine' (a treatment quaifying for routine or baseline commissioning) although any treatment that is routine would of course be standard. Interferon alfa: Is no longer considered a treatment strategy option in England although it is, in certain configurations, elsewhere in the EU	
	NHS England	No comment	Comment noted. No action required.
	Royal College of Pathologists	Comparators should be broken down by disease phase. CML CP and accn can be considered together but CML blast crisis should be included in PH+ ALL. If you include bosutinib you should include dasatinib. There is no difference in efficacy or tolerability between these two Hydroxycarbamide is not an appropriate comparator because it does not affect survival but is simply used as symptom relief. It has absolutely no efficacy in CML acceleration or blast crisis Interferon alfa is no longer used in the management of CML CP and was never used in advanced phase disease Clofarabine should be included in the comparison for advanced phase disease	Comments noted. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness

Section	Consultee/ Commentator	Comments [sic]	Action
		Consideration should be given to the inclusion of blinatumomab and Inotuzumab ozogamicin in the treatment of ALL and CML lymphoid blast crisis	• the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013). As bosutinib is available through the Cancer Drugs Fund it is considered to be current practice in the NHS. Dasatinib was removed from the Cancer Drugs Fund in November 2015 and therefore cannot be considered as current NHS practice. It is usual to include best supportive care (that is, treatment that provides symptom relief only) as a comparator to enable the benefit of an active intervention to be demonstrated

Section	Consultee/ Commentator	Comments [sic]	Action
			against treatment that provides symptom relief only. Clofarabine is not included as a comparator as its marketing authorisation in the UK is for the treatment of children only and it is not used in the treatment of Philadelphia-chromosome-positive ALL. As the relevant comparators are those treatments that are currently used in clinical practice, any new treatments that are not current practice are not included.
Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*		
	ARIAD Pharmaceuticals /Incyte Corporation	We agree that the listed outcome measures are the most relevant and important to consider	Comments noted. No action required.
	Pfizer	No comments	Comments noted. No action required
	NCRI-RCP-ACP	Yes	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		For ALL EFS is usually used	Event-free survival has now been included in the outcomes section of the scope.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	We agree with those measures set out in the draft scope but would ask that consideration be given to adding dose reduction rates because: (i) Dose reduction is increasingly becoming a factor in the design of treatment strategies for the significant number of patients able to obtain an optimal and enduring response following TKI treatment including ponatinib treatment (ii) Dose reduction is a component of two ongoing clinical trials (DESTINY which is a pilot for SPIRIT 3) with ponatinib included in the latter (iii) Dose reduction is over time strongly related to diminution of the intensity, and sometimes scope, of adverse effects accompanying treatment and brings with it a subsequent improvement of HRQoL (iv) Dose reduction has the potential to reduce the cost of treatment and, when aggregated, reduces the budget impact of TKI treatment for CML.	Comments noted. It was considered that dose reduction would not be a key outcome that would affect decision-making. No action required.
	Bristol-Myers Squibb Pharmaceuticals	We believe these are as needed and have no further comment on outcome measures.	Comment noted. No action required.
	NHS England	No comment	Comment noted. No action required.
	Royal College of Pathologists	Outcome measures for CML should include the globally accepted milestones of the ELN. In CML, it is not useful to use measurements such as 'response rates' or 'time to response' without defining the nature of the response eg. cytogenetic or he various levels of molecular response	Thank you for your comments. The means of measuring the outcomes set out in the scope are not specified, in order to keep the scope broad and not unnecessarily exclude different types of measures.
Economic	*Comments on aspects such as the appropriate time horizon.*		

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analysis	ARIAD Pharmaceuticals /Incyte Corporation	We disagree that the economic modelling should include the costs associated with diagnostic testing for T315I mutation with ponatinib, as this incorrectly implies that these patients would not otherwise have been tested. In fact: 1. European LeukemiaNet (ELN) guidelines recommend to perform a mutational analysis, which is standard and includes testing for a range of mutations of which T315I is one, in all cases of treatment failure. 2. Ponatinib is a pan BCR-ABL inhibitor and is active against native and mutated BCR-ABL, irrespective of the mutation. Therefore no T315I testing would be required in order to use ponatinib because a high efficacy has been demonstrated irrespective of the mutation status. On the contrary, mutational analysis is mandatory for all the 2G TKIs in patients failing a prior therapy, in order to identify mutations which confer resistance to the specific agent. Therefore, testing for a broad range of mutations is standard practice in England, it is supported by clinical guidelines, and as documented by EMA's approval of ponatinib - mutation testing would not be a pre-requisite for treating patients falling within ponatinib's licensed indication, based on the pivotal registration trial data demonstrating efficacy in patients with or without T315I. We agree with the proposed analysis time horizon and perspective.	Comments noted. The sentence relating to costs associated with diagnostic testing has been removed from the scope.
	Pfizer	None	Comment noted. No action required.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	No comment	Comment noted. No action required.
	Bristol-Myers Squibb Pharmaceuticals	We have no comments on the specification of the economic analysis.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	No comment	Comment noted. No action required.
	Royal College of Pathologists	Almost all the TKIs will be reviewed again by NICE as they take over the work of the CDF. It would seem reasonable to have a time-point at which NICE considers the entire patient pathway to avoid the current confusion created by CDF decisions taken in isolation and without consideration of the patient journey	Comment noted. No action required. NICE's review decision process will take into account whether a Multiple Technology Appraisal (MTA) may be appropriate at that time.
Equality and diversity	*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the remit and scope may need changing in order to meet these aims. In particular, please tell us if the remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;* • *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts*		
	Leukaemia CARE	There is currently an inequitable situation in access to ponatinib due to the different avenues of funding throughout the UK. Ponatinib, in its full license indication, is recommended for routine use in both Scotland and Wales for both CML and ALL patients. In England, however, only patients with the T315i mutation have access to the TKI through the CDF (not routinely) and as ponatinib is currently under review for patients in these settings, its future access is unclear. We feel that it is imperative that there is access via the Cancer Drugs Fund across the full indication (rather than just for T315i patients) whilst the appraisal is ongoing. As far as we are aware, this is the only drug in the CDF 'group 3' that is not being funded across its full indication whilst the appraisal	Thank you for your comments. This is acknowledged in the equality impact assessment published with the final scope.

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		takes place. It is inequitable that there is no access for these patients in England, whilst it is routinely commissioned in Scotland and Wales. As such, access is currently dependent on where in the UK you live, which is entirely unacceptable – access to ponatinib should be readily and equally available to all CML and ALL patients, throughout the UK, should they require it.	
	Pfizer	Not to our knowledge	Comment noted. No action required.
	NCRI-RCP-ACP	Patients from ethnic minorities (in whom it is difficult to find a suitable donor), patients with significant co-morbidities and elderly patients may not be eligible for allogeneic transplantation making their options more limited.	Thank you for your comments. This is acknowledged in the equality impact assessment published with the final scope.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	Please see our point (iii) included in the Allogeneic Stem Cell Transplantation part of our response for the 'Comparators' section which appears below in the last box in the Comment 2 part of this form.	Thank you for your comments. This is acknowledged in the equality impact assessment published with the final scope.
	Bristol-Myers Squibb Pharmaceuticals	We have no comments regarding equality.	Comment noted. No action required.
	NHS England	No comment	Comment noted. No action required.
	Royal College of Pathologists	Older patients and/or those from ethnic minorities will be discriminated against if the only suitable treatment is allogeneic stem cell transplant. This is more hazardous in older patients and there are considerable difficulties in finding donors for patients from ethnic minorities	Thank you for your comments. This is acknowledged in the equality impact assessment published with the final scope.

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Innovation	*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)?* *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?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*		
	ARIAD Pharmaceuticals /Incyte Corporation	Ponatinib is the first 3G TKI with a pan BCR-ABL inhibition profile, and represents a step-change in the management of CML patients who have failed treatment with a 2G TKI. In the PACE study, ponatinib was demonstrated to be effective in a substantial proportion of heavily pre-treated CML patients independently of mutational status. Only approximately 50% of CML patients have a detectable mutation, with the remainder of cases being due to unknown mechanisms. Ponatinib has demonstrated efficacy in both groups of patients. Response rates to previous therapy are usually a predictor of response to subsequent therapy. However, responses achieved with ponatinib exceeded responses achieved with the last prior TKI, generally nilotinib or dasatinib, two- to ten-fold: major cytogenetic response (MCyR) 56% and major molecular response (MMR) 39% compared to 26% and 3%, respectively. These improved response rates for ponatinib were associated with a high probability of progression-free survival (PFS) and overall survival (OS) at 4 years (57% and 77% respectively). The patients in the PACE study were the most heavily pre-treated ever studied. Ponatinib was associated with robust antileukaemic activity in this group where imatinib, nilotinib and/or dasatinib had failed. These patients had very limited options, and prior to the availability of ponatinib the only remaining treatment option offering them a reasonable chance for long-term survival was allo-SCT. Not only is this a procedure for which few patients are	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		suitable candidates, but recently published data have indicated that the duration of response with ponatinib could exceed that seen with allo-SCT in patients with CP-CML and the T315I mutation.	
	Leukaemia CARE	We would consider all TKI's to be innovative. It is particularly innovative for patients with the T315i mutation, as data shows that it is the only TKI that is effective for patients with the T315i mutation. Because each TKI works differently, and there has been a shift towards more personalised treatment, we would argue that it is important that ponatinib was available to as many CML and ALL patients as possible, to ensure that they have a number of "insurance" treatment options, should their current one stop working. Furthermore, in clinical trials ponatinib has demonstrated "significant antileukemic activity across categories of disease stage and mutation status". In the phase 2 trial, ponatinib continued to "exhibit deep and durable responses with up to 6 years follow up".	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
	Pfizer	No comments	Comment noted. No action required.
	NCRI-RCP-ACP	Yes A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. Cortes JE, et al; PACE Investigators. N Engl J Med. 2013 Nov 7;369(19):1783-96. doi: 10.1056/NEJMoa1306494. Epub 2013 Nov 1. Efficacy and safety of ponatinib in CP-CML patients by number of prior tyrosine kinase inhibitors: 4-year follow up of the Phase 2 PACE Trial. Hocchaus A, et al; PACE Investigators. ASH 2015. Blood 2015; 124: abstract 4025.	Comment noted. No action required.
	The Chronic Myeloid Leukaemia Suport Group (CMLSg)	Whilst we accept that there is no case to be made for considering that ponatinib qualifies for 'step change' status in the manner accorded to imatinib well over a decade ago, we do consider it to provide a solution to the considerably narrower problem of the discovery of a TKI effective against a mutation all other TKIs lack an effect against. In that sense ponatinib has	Comments noted. The potential innovative nature of the technology will be considered by the appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
		proved innovative.	committee.
	Bristol-Myers Squibb Pharmaceuticals	None.	Comment noted. No action required.
	NHS England	No comment	Comment noted. No action required.
	Royal College of Pathologists	Yes, ponatinib is a step-change in the management of patients with CML and some with ALL. This third generation agent is not only the only drug with efficacy against the T315I mutation, but also salvages about 40% of patients with CML-CP who have failed 3 or 4 other TKI. This salvage has a considerable impact on life expectancy, giving the patients many years of good quality life	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
Other considerations	Pfizer	None	Comment noted. No action required.
	The Chronic Myeloid Leukaemia Support Group (CMLSg)	Additions to the comparators section: Allogeneic stem cell transplantation (SCT): We do not object to its comparator status provided there is an acknowledgement that: (i) It remains a treatment option available only to those patients judged by specialist clinicians to be clinically suitable for what is acknowledged to be a high risk procedure. (ii) It also remains a treatment option available only to those patients for whom a matched and willing donor can be located. (iii) It is well documented that BAME patients are seriously disadvantaged compared to Caucasian patients in the search for a matched donor. (iv) Our observation, based on over a decade operating as a charity, is that patients overwhelmingly view SCT as a last line of treatment option after all licensed TKIs have been considered. That is the TKIs have either been tried, discounted or proved to be inaccessible as treatment options . The description of SCT as the only 'curative' treatment option for CML should not lead to an assumption that patients are behaving irrationally in ascribing SCT to last line of treatment status.	Thank you for your comments. The features of allogeneic stem cell transplantation are addressed in the background section of the scope and the equality impact assessment published alongside it. It is usual to include best supportive care (that is, treatment that provides symptom relief only) as a comparator to enable the benefit of an active intervention to

Section	Consultee/ Commentator	Comments [sic]	Action
		(v) Assessing the cost effectiveness of an SCT should acknowledge the known difficulties surrounding establishing costs including the variety of clinical approaches available and post SCT hospital re-admission costs especially those associated with graft versus host disease. Best Supportive Care (BSC): (i) NICE appraisals of treatments for CML over the last decade have only referred to hydroxycarbamide (HU) in discussions of BSC. (ii) Because its action is not capable of securing a cytogenetic (or molecular) response HU has been recognised to have no effect on the natural history of CML, a fatal disease if left untreated. (iii) HU has proved difficult to define in a NICE TA environment. It has been described as an agent used between treatments, as a palliative agent, as a precursor agent to (particularly a 1st) TKI treatment and as a treatment for CML even whilst it is recognised it has no impact on the biology of the disease. In our opinion, granting treatment status to HU triggers an unproductive and irresolvable discussion of likely survival times resulting from its use; in particular when its deployment is tied to various lines in the treatment pathway. Whilst we recognise the driver in play we do not think, as it has so often in the past, this issue should be allowed to dominate appraisal	be demonstrated against treatment that provides symptom relief only.
	Bristol-Myers Squibb Pharmaceuticals	None.	Comment noted. No action required.
	NHS England	No comment	Comment noted. No action required.
	Royal College of Pathologists	Please try to consider all these drugs together. With the support of the NCRI CML sub-group the creation of an algorithm for patient treatment, would make a lot of sense. This would demonstrate not only a logical approach to treatment but also reassure NHS England of the relatively small number of patients being moved to successively more potent (and probably more expensive) agents. There should also be guidelines for discontinuation of treatments that cannot improve patient survival	Thank you for your comments. Ponatinib has been referred to NICE as a Single Technology Appraisal (STA), to ensure timeliness in terms of

Section	Consultee/ Commentator	Comments [sic]	Action
			producing guidance on treatments in transition from the Cancer Drugs Fund. However, the review decision process will take into account whether a Multiple Technology Appraisal (MTA) may be appropriate at that time.
Questions for consultation	*Question: Is the use of ponatinib conditional on the presence of T3151 mutation?*		
	ARIAD Pharmaceuticals /Inctye Corporation	Answer: No. Ponatinib is approved for the treatment of CML patients in any phase of the disease, where a 2G TKI has failed, irrespective of their mutational status. Ponatinib is a potent oral TKI that is active against unmutated and mutated BCR-ABL, including but not limited to the T315I mutation. Ponatinib activity in the subset of patients who present with the T315I mutation should be considered an additional benefit provided by ponatinib. In fact, in the PACE study, the T315I mutation was present in only 26% of the CML patients, and a multivariate analysis indicated that T315I was not a significant predictor of a major cytogenetic response. Other features, especially higher dose intensity and younger age in patients with the T315I mutation explain the different response rates versus those without the mutation. High response rates were observed among patients with chronic-phase CML regardless of mutation status, and responses were observed for each of the 15 mutations present in more than one patient at baseline (Cortes et al. NEJM 2013;369(19):1783-96).	Comments noted. No action required.
	NCRI-RCP-ACP	The use of ponatinib should not be conditional on the presence of the T315I mutation.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		The issue above, conditional on T315I is also relevant to ALL. T315I almost always arise after dasatinib therapy and as previously mentioned, dasa is not readily available.	
	Question: Is the diagnostic testing for T315I mutation considered to be established clinical practice in the NHS?		
	ARIAD Pharmaceuticals /Incyte Corporation	Answer: Yes. T315I mutation testing is part of the mutational analysis panel, which is standard practice in the NHS. Indeed, whereas T315I testing would be essential for all other TKIs, in order to exclude the adoption of an ineffective therapy, this is not needed for ponatinib, since it is active against this mutation and all other mutations, as well as native BCR-ABL.	Comments noted. The sentence relating to costs associated with diagnostic testing has been removed from the scope.
	NCRI-RCP-ACP	Diagnostic testing for the T315I mutation at selected UK laboratories is considered to be established clinical practice in the NHS.	Comments noted. The sentence relating to costs associated with diagnostic testing has been removed from the scope.
	Question: Where do you consider ponatinib will fit into the existing NICE pathway?		
	ARIAD Pharmaceuticals /Incyte Corporation	Answer: Ponatinib should be the treatment of choice in all CML patients who fail a 2G TKI and where imatinib is not clinically appropriate. Ponatinib should not be restricted to use in the post–third-line setting because the current third-line practice of recycling 2G TKIs in patients who have already failed 2G TKI therapy has been demonstrated to offer limited clinical benefit and exerts selective pressure resulting in clones that maintain a higher degree of resistance to treatment. Indeed, neither dasatinib nor nilotinib are approved for sequential use after each other, reflecting the poor results observed in studies after failure of therapy with more than one prior TKI. Thus, use of ponatinib across the indicated population would avoid the inefficient use of NHS resources and the unnecessary risks accociated with the recycling 2G TKIs.	Comments noted. No action required.
	NCRI-RCP-ACP	In terms of the existing NICE pathway, I believe ponatinib would fit as follows: Any patient with a T315I mutation should receive ponatinib regardless of line of therapy. For patients without a T315I mutation – likely to be third line after	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		failure (resistance) of at least 2 TKIS of which at least one should be a second line TKI – dasatinib, nilotinib or bosutinib. For failure due to intolerance – probably a minimum of 4th line.	
	Question: Is the population defined appropriately; in particular should the population with the T315I mutation be considered as a separate population?		
	ARIAD Pharmaceuticals /Incyte Corporation	ALL: Answer: No, the population with the T315I mutation should not be considered as a separate population. Ponatinib is approved for the treatment of Ph+ ALL, where dasatinib has failed, irrespective of patients' mutational status. Ponatinib is a potent oral TKI that is active against unmutated and mutated BCR-ABL, including but not limited to the T315I mutation. Ponatinib activity in the subset of patients who present with the T315I mutation should be considered an additional benefit provided by ponatinib. In fact, in the PACE study, the T315I mutation was not present in many of the Ph+ALL patients enrolled. Moreover, multivariate analyses of the full PACE study population, including the Ph+ALL cohort, indicated that T315I was not a significant predictor of response. Other features, especially higher dose intensity and younger age in patients with the T315I mutation explain the different response rates observed between those with and without the mutation. Finally, given the rarity of adults with refractory (i.e. after dasatinib failure) Ph+ALL disease, the generally poor prognosis, the small sample (n=32) of Ph+ALL patients in the ponatinib PACE pivotal trial, the lack of alternative options (other than transplant or supportive/palliative care) for refractory patients, and the overall paucity of data in the published literature concerning refractory Ph+ALL with or without T315I, any additional stratification of an already limited dataset would simply create further uncertainty in the clinical and cost-effectiveness analyses.	Comments noted. No action required.
	NCRI-RCP-ACP	It would be anticipated that a higher proportion of patients with a T315I mutation would respond to ponatinib, compared to those without a T315I mutation – in the PACE study, in the primary analysis at a median of 15 months, 70% of patients with a T315I mutation achieved major cytogenetic response to ponatinib compared to 51% of patients without a T315I mutation.	Comment noteds. No action required.

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		However, both response rates are impressive.	
	Pfizer	CML As per previous comments, patients with the T315I mutation should be considered as a separate subpopulation, as they have different possible pathways and subsequent management	Comment noted. No action required.
	Pfizer	As per previous comments, patients with T315I mutation should be considered separately	Comment noted. No action required.
	Leukaemia CARE	We would suggest that the appraisal considers ponatinib as an effective treatment for ALL patients whose all other options have been exhausted and not just for those with the T315i mutation. In recommending the treatment for this patient group alone would create an inequitable situation.	Comments noted. No action required.
	NHS England	We believe that the population with the T315I mutation be considered as a separate population. The CDF considered that there was no alternative treatment in this specific group and that the drug therefore fulfilled the CDFs "unmet need" criteria.	Comments noted. No action required.
	Royal College of Pathologists	I am not a particular expert in ALL but in general I would not separate patients with the T315I mutation from those without the mutation. In general none of the TKIs, including ponatinib, have durable efficacy in relapsed/refractory Ph+ALL or CML blast crisis, so a separation creates unnecessary work for the appraisal – these drugs are largely used as a bridge to transplant, or in patients unsuitable for transplant, as a means of exerting temporary control over disease using oral agents. This allows the terminal patient to spend time outside the hospital whereas the current treatments of intensive chemotherapy usually result in many weeks or months as in-patients. This might also be acknowledged in the endpoints which in this group of patients could include hospital costs T315I mutation detection can be accurately performed in HMDS laboratories throughout the UK	Comments noted. No action required. Comment noted. The sentence relating to costs associated with diagnostic testing has been removed from the scope.

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		I have already commented on comparators for Ph+ALL but included CML lymphoid blast crisis with these. Established clinical practice for ALL is acute leukaemia-like chemotherapy (usually FLAG-Ida or CLAG-Ida, or Hyper CVAD)	Comment noted. Please see previous response.
	Question: Is the diagnostic testing for T315I mutation considered to be established clinical practice in the NHS for people with ALL?		
	ARIAD Pharmaceuticals /Incyte Corporation	Answer: Yes it is. As noted in our prior comments to the original CML draft scope, T315I mutation testing is part of the mutational analysis panel, which is standard practice in the NHS. Indeed, whereas T315I testing would be essential for all other TKIs, in order to exclude the adoption of an ineffective therapy, this is not needed for ponatinib, since it is active against this mutation and all other mutations, as well as native BCR-ABL.	Comments noted. The sentence relating to costs associated with diagnostic testing has been removed from the scope.
	Question: Should clofarabine (as a bridge to bone marrow transplant) be included as a comparator?		
	ARIAD Pharmaceuticals /Incyte Corporation	Answer: No it should not. There is very limited published evidence on clofarabine in adult ALL and virtually no evidence of clofarabine in Ph+ ALL, specifically. The licensed indication for clofarabine is for patients under 21 years of age. The pivotal registration trial for clofarabine was not limited to Ph+ patients. In contrast, the indication for ponatinib is for Ph+ALL adults, only. As a result, there is insufficient data to conduct a clinical or cost-effectiveness analysis to compare these two interventions.	Comment noted. No action required.
	Leukaemia CARE	Clofarabine, currently funded for relapsed or refractory ALL patients on the CDF, is currently being reviewed. As such its availability as a follow up treatment for patients in this setting is unclear.	Comment noted. No action required.
	Question: Which treatments are considered to be established clinical practice, AND, how should 'established clinical management without ponatinib' be defined?		
	ARIAD Pharmaceuticals /Incyte	Answer: The standard of care for adult patients with Ph+ ALL is induction therapy including a tyrosine-kinase inhibitor (TKI), followed by allogeneic stem cell transplantation (allo-SCT) in suitable patients for whom a donor can	Comments noted. No action required.

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	Corporation	be identified. This represents the only potentially curative treatment. Allo-SCT yields better outcomes when performed in patients with BCR-ABL transcripts below the detectable level of minimal residual disease (MRD), as patients with a measurable level of MRD pre-transplant have a significantly higher risk of post-transplant relapse. Therefore, achieving a complete remission (CR) is crucial to the long-term success of allo-SCT. At present, ponatinib is the only TKI licenced for patients with Ph+ ALL in whom imatinib and dasatinib have failed to induce a complete response. Therefore, in the absence of ponatinib, the clinical management of adults with Ph+ALL who have failed imatinib and dasatinib or who have the T315I mutation is limited to allo-SCT (following induction), best supportive care (vincristine and prednisone) or investigational agents being studied in clinical trials.	
	Question: Where do you consider ponatinib for the treatment of ALL will fit into the existing NICE pathway?		
	ARIAD Pharmaceuticals /Incyte Corporation	Answer: In the UK, ponatinib will be used at first or subsequent relapse, in patients for whom transplant may or may not be an option, in accordance with its label that requires patients to have failed treatment with dasatinib prior to ponatinib initiation. As noted above, the treatment strategy recommended in guidelines for relapsed Ph+ALL adults entails transplantation (subject to patient fitness, donor availability, and effectiveness of the chosen pre-SCT induction strategy), enrolment in clinical trials if possible, or supportive/palliative care.	Comments noted. No action required.
Additional comments on the draft scope	Pfizer	References (1) Ponatinib: Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/medicine/28145 Accessed 24th June 2016	Comment noted. No action required.
	Bristol-Myers Squibb Pharmaceuticals	None.	Comment noted. No action required.
	Royal College of	I have a concern about using the same incremental QALY to assess CML in	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pathologists	general as opposed to the very few patients who fail the first and second generation TKI. I understand the need to consider cost-effectiveness and the inevitable requirement to reduce or constrain NHS spending but the landscape of CML has changed so considerably over recent years, that I think the assessments should also change. For instance, about 50-60% of patients will respond durably to imatinib. Generic imatinib will be available in the UK at the end of 2016 and will cut costs for treatment for CML by a significant amount. Of the 40% of patients who do not respond to imatinib, about half will respond to one or other of dasatinib, nilotinib or bosutinib. Generic forms of these drugs will eventually follow imatinib, This leaves about 20% of the total population of patients presenting in chronic phase. About 40% of these will respond to ponatinib: response will be clear within 6 months of starting treatment and non-responders should discontinue ponatinib and be referred for transplant as soon as possible. We are now left with fewer than 10% of the original cohort of patients who need ponatinib. Some will not tolerate the drug long-term, so eventually about 5% of the total population will beneft from on-going ponatinb. These patient seem to respond durably so they are restored to a near-normal or normal life expectancy – this is not the same as putting a patient into remission for a few months. These aspects do not seem to be taken into consideration when making decisions – instead the decision is based on QALYs that are the same for 80% as for 5%. I have never seen an analysis that addresses starting a drug but not continuing it which is the reality for about 75% of patients who start ponatinib. I also feel very strongly that outcome data from patients who receive these effective but very high cost drugs should be collected within a registry so that we have some measure of the effects (medical and financial) of our decisions	Submissions to NICE should include an analysis of results generated using NICE's reference case methods which includes a cost utility analysis in which the health effects are expressed as QALYs. NICE's reference case also specifies that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. Many technologies have impacts on costs and outcomes over a patient's lifetime. In such instances, a lifetime time horizon for clinical and cost effectiveness is usually appropriate. A lifetime time horizon is required

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			when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life. A time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between treatment options, and the differences in costs and health-related quality of life relate to a relatively short period. Please see section 5 of NICE's guide to the methods of technology appraisal (2013). Any uncertainty regarding the clinical and cost-effectiveness of ponatinib will be considered by the appraisal committee. No action required.

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

Department of Health