**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Ibrutinib for treating chronic lymphocytic leukaemia**

**Response to consultee and commentator comments on the draft scope (post-referral)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | Cochrane Haematological Malignancies Group | Yes | Comment noted. No action required. |
| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | Otherwise accurate but incomplete.<br>There is a need to clarify further the toxicity of current treatments, the chronic nature of CLL and the difficulty in treating relapsed disease<br>Patients with CLL may live with a considerable burden of symptoms impacting their quality of life. This is true in both 'watch and wait' and relapsed groups of patients. | Thank you for this information. The Appraisal Committee will consider carefully the nature of CLL, the side-effects of treatment and the quality of life of people with CLL. The background section of the scope is intended to provide a brief introduction to the |

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| | | | disease. No action required. |
| | Janssen | No further comment. | No action required. |
| | Leukaemia CARE | We have a number of comments to make regarding the background information.<br>We would like reference to be made to 'watch and wait', in order to give greater insight to living with chronic lymphocytic leukaemia (CLL). Many patients diagnosed with early-stage CLL will have few symptoms and are therefore monitored regularly for disease progression (which is referred to as 'watch and wait'). A proportion of patients will undergo 'watch and wait' and their disease will never progress enough to require treatment. As such, the numbers of patients requiring treatment may be less than the incidence of CLL might suggest.<br>Additionally, many patients diagnosed with CLL will experience feelings of fear, shock or even hopelessness. We would also like reference to be made to the emotional impact of a diagnosis of CLL on patient's physical and emotional wellbeing. | Thank you for this information. NICE understands that 'watch and wait' is unlikely to be used as a treatment strategy for the population in the appraisal (that is, people who have received at least 1 therapy or who have 17p deletion or TP53 mutation). During the appraisal, the Committee will consider carefully the impact of CLL on people's quality of life. The background section of the scope is intended to provide a brief introduction to the disease. No action required. |
| | Roche Products | The first population may be more accurately described as:<br>People who have **relapsed** after at least 1 prior therapy | Comment noted. The scope is based on the wording of the |

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| | | | therapeutic indication in the summary of product characteristics for ibrutinib. No action required. |
| | Roche Products | Treatment options for this population should state Idelalisib plus rituximab (as per the comparators listed) | Comment noted. The draft scope stated 'idelalisib in combination with rituximab.' No action required. |
| | | | |
| The technology/ intervention | Cochrane Haematological Malignancies Group | *Is the description of the technology accurate?*<br>Yes | Comment noted. No action required. |
| | Gilead Sciences | Yes, please confirm this appraisal refers to ibrutinib monotherapy only. | In the summary of product characteristics for ibrutinib, the wording of the therapeutic indication does not include specific treatment combinations. As noted in the scope, guidance will be issued in the context of the evidence that has underpinned the |

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| | | | marketing authorisation granted by the regulator. No action required. |
| | CLL Support Association | Ibrutinib (Imbruvica, Janssen) is an oral inhibitor..... which ***aims*** to stop B-cell proliferation and promote cell death.<br>From our previous scope submission: : Bruton's Tyrosine Kinase inhibitor regulates various pathways for cell proliferation, cell death and migration | The draft scope stated that ibrutinib is an oral inhibitor of Bruton's Tyrosine Kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death. No action required. |
| | Janssen | Yes. | No action required. |
| | Leukaemia CARE | No comments. | No action required. |
| | Roche Products | No comments. | No action required. |
| | | | |
| Population | Cochrane Haematological Malignancies Group | What is meant by: for whom chemo-immunotherapy is not suitable? | This phrase is taken from the wording of the therapeutic indication in the summary of product characteristics for ibrutinib. The Appraisal Committee will discuss how 'unsuitable for |

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| | | | chemo-immunotherapy' was defined in the clinical trials for ibrutinib and how this group of patients could be defined in clinical practice. No action required. |
| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | Adults who have received at least one prior therapy **and have relapsed or are refractory?** | Comment noted. The population in the scope reflects the marketing authorisation for ibrutinib. No action required. |
| | Janssen | Yes the population is defined appropriately. | No action required. |
| | Leukaemia CARE | No comments. | No action required. |
| | Roche Products | The first population may be more accurately described as:<br>Adults with chronic lymphocytic leukaemia who have **relapsed** following at least 1 prior therapy | Comment noted. The population in the scope reflects the marketing authorisation for ibrutinib. No action required. |
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| Comparators | Cochrane Haematological Malignancies Group | In the table are more comparators listed (e.g corticosteroids, best supportive care) than in the background text above | Comment noted. Additional text has been added to the background section. |
| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | No one therapy can be described as 'best alternative care' as each patient situation is different.<br>It is unlikely that FCR would be used for many relapsed CLL patients due to acquired toxicity, additional deletions and comorbidities, as the average age at diagnosis is 72.<br>There is no definitive evidence for the selection of therapy in relapsed/refractory CLL, it remains clinicians choice dependent on the overall fitness of the patient and the nature of their disease progression. | Comments noted. During scoping, NICE aims to create an inclusive list of the treatments that are part of established practice in the NHS. The Appraisal Committee will discuss whether each of these treatments is an appropriate comparator for ibrutinib, based on the evidence and advice from patient and clinical experts. No action required. |
| | Janssen | The proposed comparators are acceptable, although it should be noted that data for most regimens in r/r CLL are very sparse.<br>With respect to the CLL population who have received at least 1 prior therapy, it is further proposed that ofatumumab should remain as a comparator. Ofatumumab is licenced for the treatment of r/r CLL and is a recognized standard of care in r/r CLL, approved in both the United States | Comments noted. NICE technology appraisal guidance 202 does not recommend ofatumumab for treating chronic lymphocytic leukaemia (CLL) that is |

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| | | and the EU (and in Canada, Japan, Australia, Israel, Switzerland, Argentina and Latin American countries) for fludarabine and alemtuzumab-refractory CLL. Ofatumumab is included as a treatment option in international guidelines (NCCN/ESMO) as well as in the British Committee For Standards in Haematology (BCSH) guidelines for CLL. It was also recently approved in combination with chlorambucil for treatment naïve CLL in the U.S. and in Europe. Ofatumumab is the regimen for which ibrutinib has direct comparative evidence and as such its inclusion is considered important for this appraisal. | refractory to fludarabine and alemtuzumab. Ofatumumab for relapsed or refractory CLL was removed from the Cancer Drugs Fund list in March 2015. Accordingly, ofatumumab is not considered to be part of established NHS practice for adults with CLL who have received at least 1 prior therapy, and therefore it is not a comparator. No action required. |
| | Leukaemia CARE | We would like to highlight that in this setting there is no agreed standard of care and the best treatment option will depend upon each patient's individual situation. | Comment noted. During scoping, NICE aims to create an inclusive list of the treatments that are part of established practice in the NHS. The Appraisal Committee will discuss whether each of these treatments is an appropriate comparator for ibrutinib, based on the evidence and advice from patient and |

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| | | | clinical experts. No action required. |
| | Leukaemia CARE | We feel that it is important to consider that some patients (who are less fit or have comorbidities) will be unsuitable for or unable to tolerate some of the more aggressive comparator treatment options. As such, ibrutinib may have particular benefit for this group of patients. | Comments noted. If your organisation has evidence that ibrutinib is more effective or cost effective in subgroups such as those with comorbidites, please include this information in your submission to NICE. No action required. |
| | Leukaemia CARE | We would like clarification regarding the appropriateness of ofatumumab as an additional comparator (with reference to clinical practice) for patients with mutations (such as the 17p deletion or TP53 mutation). | Comment noted. NICE has not received any consultation responses suggesting that ofatumumab is part of established NHS practice for adults with 17p deletion or TP53 mutation, and therefore it is not a comparator in the scope. No action required. |
| | Roche Products | Ofatumumab is a valid comparator for relapse patients, it should be noted that the ofatumumab licensed indication in refractory CLL, is for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab. However post March 2016 this indication is no longer funded on the CDF. | Comment noted. NICE technology appraisal guidance 202 does not recommend |

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| | | | ofatumumab for treating chronic lymphocytic leukaemia (CLL) that is refractory to fludarabine and alemtuzumab. Ofatumumab for relapsed or refractory CLL was removed from the Cancer Drugs Fund list in March 2015. Accordingly, ofatumumab is not considered to be part of established NHS practice for adults with CLL who have received at least 1 prior therapy, and therefore it is not a comparator. No action required. |
| | Roche Products | Rituximab monotherapy should be added as a comparator in relapse | Comment noted. A comparator of rituximab alone (for people with refractory disease) has been added to the scope. |
| | Roche Products | In treatment naïve patients all of the comparators listed in questions for consultation are relevant for comparison. | Comment noted. Other consultees advised that the comparators in the draft scope were |

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| | | | appropriate for adults with 17p deletion or TP53 mutation. No action required. |
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| Outcomes | Cochrane Haematological Malignancies Group | *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*<br>Yes, however, OS, Adverse events and HRQoL are the more important ones compared to the others | Comment noted. The listed outcomes are included in the scope and will be discussed by the Appraisal Committee. No action required. |
| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | Yes | No action required. |
| | Janssen | Janssen believes this is an appropriate set of outcomes. | No action required. |
| | Leukaemia CARE | No comments. | No action required. |
| | Roche Products | No comments. | No action required. |
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| Economic analysis | Cochrane Haematological Malignancies | No comments. | No action required. |

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| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | Gilead operate an Early Access Scheme for CLL patients with 17p deletion, this should be taken into account in the economic analysis and modelling. | Thank you for this information. Please include further details in your submission to NICE. |
| | Janssen | The economic analysis section states that for drugs funded by the CDF, the economic modelling should use the cost incurred by the Cancer Drug Fund. The full list price of idelalisib is likely not charged to the CDF and Janssen is not aware of what price is offered.<br>As a member of the ABPI, Janssen cannot support the use of discount prices in HTA submissions, and believe that modelling using UK list price is appropriate. The discounts of branded drugs from other manufacturers are confidential and we will respect that confidentiality. Likewise, Janssen would not break the confidentiality of discounts offered on its drugs for economic modelling by other manufacturers. | Comments noted. This text has been deleted. |
| | Leukaemia CARE | No comments. | No action required. |
| | Roche Products | No comments. | No action required. |
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| Equality and Diversity | Cochrane Haematological Malignancies | No comments. | No action required. |

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| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | No changes needed. | No action required. |
| | Janssen | No comment. | No action required. |
| | Leukaemia CARE | No comments. | No action required. |
| | Roche Products | No comments. | No action required. |
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| Innovation | Cochrane Haematological Malignancies Group | No comments. | No action required. |
| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | Yes.<br>This would provide a step change in the management of CLL and an effective treatment for hard to treat groups that have few or no treatment options available to them.<br>This step change has the potential to provide an improvement in patient experience during therapy and to result in excellent QOL, prolonged remissions and lower toxicity which could increase the number of further | Thank you for this information. The Appraisal Committee will discuss all the potential benefits of ibrutinib. No action required. |

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| | | available therapeutic options.<br><br>As an oral drug it has many advantages over all current therapies which involve frequent hospital visits for treatment with infusions and the inherent risk of infection whilst within the hospital environment. Patients who have an oral drug are less anxious that those who require infusions and develop a better relationship with their consultant.<br><br>All current therapies for the re-treatment of relapsed CLL are likely to provide shorter and shorter periods of remission and introduce more and more toxicity. These negative effects appear to be absent with Ibrutinib. | |
| | Janssen | Janssen believes that ibrutinib, as the first in class Bruton's tyrosine kinase inhibitor, is highly innovative, as it is specifically designed to inhibit a key molecular target that is critical to the disease. This is in contrast to traditional chemotherapy agents that indiscriminately affect both cancerous and normal cells.<br><br>Ibrutinib represents a step-change in efficacy and tolerability in the treatment of r/r CLL for the reasons described above and various additional factors which further demonstrate the innovative nature of this treatment:<br><br>a) The innovative mechanism of action is the underlying reason for the increased efficacy compared to current therapies used in r/r CLL – median PFS has not been reached in ibrutinib patients with 44 months follow-up in the Phase 2 trial and has not been reached in the 16 months follow-up of the Phase 3 trial (vs. 8.3 months median PFS for the comparator arm, ofatumumab). As a non-genotoxic agent, the efficacy of ibrutinib is comparatively far greater in patients with adverse cytogenetic risk factors such as 17p deletion and TP53 mutation - median PFS of these ibrutinib patients is 32.4 months from the 44 month follow-up data in the Phase 2 trial while median PFS of comparators in this high-risk patient group is <6 months (median PFS of 3.3 months on ofatumumab, 5.0 months on FCR, 4.8 months on BR, and 5.8 months of alemtuzumab). | Thank you for this information. The company is invited to include evidence of innovation in its submission. No action required. |

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| | | b) Ibrutinib's mode of action and pharmacokinetic profile contributes to its favourable tolerability; the drug is rapidly cleared from the bloodstream and consequently, off-target effects are minimal<br><br>c) Ibrutinib avidly binds to its molecular target, allowing for a once daily oral administration. It is a monotherapy and spares patients from the additional toxicity and administration requirements born by chemotherapy and other anti-cancer agents.<br><br>d) As ibrutinib is an oral monotherapy, the avoidance of chemotherapy and the reduction in hospital visits is of significant benefit to the NHS and carers as this allows for reduced health care resource use as well as reduced burden usually associated with management of toxic agents (e.g. requirements for administration in hospital or supervised administration).<br><br>e) Finally, ibrutinib as an oral monotherapy has a beneficial effect on the patient experience (e.g. less time in hospital) and their quality of life. Furthermore, for those patients who do not have carers, they are able to avoid the considerable burden of attending hospital clinics for injections and infusions alone and without support. | |
| | Leukaemia CARE | We consider the use of ibrutinib, a tyrosine kinase inhibitor, to be innovative in the treatment of CLL.<br><br>In particular we feel that ibrutinib offers a step-change in treatment for hard to treat groups that currently have limited treatment options.<br><br>As such, we feel that an appraisal of ibrutinib is appropriate. | Thank you for this information. The Appraisal Committee will discuss all the potential benefits of ibrutinib. No action required. |
| | Roche Products | No. Idelalisib also inhibits the B-cell receptor earlier in the pathway than Ibrutinib.<br><br>Ibrutinib offers an additional treatment choice for the adults with CLL and TP53 mutation or 17p deletion and for those who have relapsed after at least | Comments noted. No action required. |

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| | | one prior therapy. | |
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| Other considerations | Cochrane Haematological Malignancies Group | What is meant: if the evidence allows the following subgroups will be considered? Isn't 17p del/TP53 mutation a second, different analysis, with other comparators compared to the analysis in relapsed or refractory patients? | Comment noted. One population in the appraisal is 'adults with untreated chronic lymphocytic leukaemia associated with 17p deletion **or** TP53 mutation for whom chemo-immunotherapy is not suitable.' If evidence allows, subgroups of this population will be considered, defined by:<br>• Presence or absence of 17p deletion;<br>• Presence or absence of TP53 mutation.<br>No action required. |
| | Gilead Sciences | No comments. | No action required. |
| | CLL Support Association | There will be specific benefit for those who have certain deletions, such as 17p and 11q, and those for whom cytotoxic therapies are not suitable, those | Comments noted. Subgroups with 17p |

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| | | with significant morbidities, particularly the elderly. | deletion or TP53 mutation were included in the scope. If your organisation has evidence that ibrutinib is more effective or cost effective in additional subgroups (such as those with 11q deletion and those for whom cytotoxic therapies are not suitable), please include this information in your submission to NICE. No action required. |
| | Janssen | With respect to the subgroup “presence or absence of TP53 mutation”, no clinical data are currently available for ibrutinib and for most of the comparators considered; thus, evidence would not allow this subgroup to be considered.<br>Furthermore, while testing for the presence or absence of 17p deletion is a standard test for CLL patients within UK practice, testing for TP53 mutation is not standard practice in the UK and as such, data are scarce. | Comments noted. The scope states that these subgroups will be considered only if there is sufficient evidence. No action required. |
| | Leukaemia CARE | No comments. | No action required. |
| | Roche Products | In the definition of subgroups within the draft scope, there is reference to 2 sub-groups of 17p deletion and TP53 mutation in adults with CLL who have received at least one prior therapy. We believe that this should read | Thank you. The scope has been amended. |

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| | | previously untreated. | |
| | Roche Products | The published data on the pivotal trial (Byrd NEJM 2013) shows the median number of prior treatments were 4. It would be appropriate to consider if the clinical or economic benefit differs depending on the number of prior lines of therapy. | Comment noted. The Appraisal Committee will discuss the prior treatments received by patients in the trials and whether this affects the generalisability of the results to the NHS. No action required. |
| NICE Pathways [Delete section if not relevant] | Janssen | Ibrutinib would fit into the existing NICE pathway as per its licenced indication. Data from clinical studies (RESONATE, HELIOS) suggest that its efficacy and safety profile is consistent across the various patient populations within the r/r setting, from those with medium-risk disease and/or good general conditions to those with high-risk aggressive disease and/or poor general conditions. This is in contrast with the traditional treatments which exhibit poor efficacy in high-risk disease as well as high levels of toxicity in compromised patients.<br><br>RESONATE (pivotal phase 3 trial) more specifically demonstrates that ibrutinib monotherapy is efficacious even in difficult to treat and refractory patients. It can therefore be surmised that the efficacy would be correspondingly greater in the less refractory and more responsive patient groups. Again, this is in contrast to the currently available treatment options for r/r CLL that have moderate efficacy in the fitter patient groups but result in little response in the more refractory and difficult to treat patients. | Comments noted. The company is invited to include the relevant evidence in its submission. No action required. |
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| Questions for | Cochrane | No comments. | No action required. |

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| consultation | Haematological Malignancies Group | | |
| | Gilead Sciences | No comments. | No action required. |
| | Janssen | *1. Have all relevant comparators for ibrutinib been included in the scope?*<br>No all relevant comparators have not been included - in the r/r CLL population, ofatumumab should be included as a comparator for reasons outlined previously. | Comments noted. NICE technology appraisal guidance 202 does not recommend ofatumumab for treating chronic lymphocytic leukaemia (CLL) that is refractory to fludarabine and alemtuzumab. Ofatumumab for relapsed or refractory CLL was removed from the Cancer Drugs Fund list in March 2015. Accordingly, ofatumumab is not considered to be part of established NHS practice for adults with CLL who have received at least 1 prior therapy, and therefore it is not a comparator. No action required. |
| | Janssen | *Which treatments are considered to be established clinical practice in the* | Comments noted. |

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| | | *NHS for CLL?*<br>Currently, there is no single established clinical practice in the NHS for the treatment of r/r CLL. There are a number of different available treatment options (including BR and ofatumumab) but the BCSH guidelines on CLL recommend that patients in this setting should be offered enrolment to clinical trials: "In view of the increasing number of new agents showing significant activity in phase 2 trials, and the extensive portfolio of trials now available in the UK, patients should be offered entry into clinical trials wherever possible". The lack of an established standard of care in CLL within the NHS is clearly demonstrated by this guidance recommending trial enrolment. | During scoping, NICE aims to create an inclusive list of the treatments that are part of established practice in the NHS. The Appraisal Committee will discuss whether each of these treatments is an appropriate comparator for ibrutinib, based on the evidence and advice from patient and clinical experts. No action required. |
| | Janssen | *Is rituximab monotherapy part of established clinical practice in the NHS for CLL?*<br>No it is not. | Comment noted. NICE heard from another consultee that rituximab monotherapy may be used for refractory disease. Accordingly, it has been added to the scope as a comparator. |
| | Janssen | *Are any of the following treatments a part of established clinical practice in the NHS for previously untreated CLL associated with 17p deletion or TP53 mutation?*<br>*o Bendamustine (with or without rituximab)*<br>*o Chlorambucil (with or without rituximab)* | Comment noted. No action required. |

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| | | *o Ofatumumab in combination with bendamustine or chlorambucil*<br>*o Obinutuzumab in combination with chlorambucil*<br>No, [these] treatments are not a part of established clinical practice associated with this subgroup, whose disease responds poorly to genotoxic agents. | |
| | Janssen | *Is best supportive care defined appropriately in the scope?*<br>Yes. | Comment noted. No action required. |
| | Janssen | Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom ibrutinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?<br>*Please see comments in response to "other consideration" in section "Comment 1: the draft scope" about subgroups; no there are no other subgroups of interest.* | Comment noted. No action required. |
| | Janssen | *Please tell us if the proposed remit and scope:*<br>• *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ibrutinib is licensed.* **No**<br>• *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.* **No**<br>• *could have any adverse impact on people with a particular disability or disabilities.* **No**<br>*Please tell us what evidence should be obtained to enable the Committee to* | Comment noted. No action required. |

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| | | *identify and consider such impacts.*<br>We would suggest that the committee looks to obtain opinions from patient groups who have had experience with ibrutinib in order to identify and consider such impacts. | |
| | Janssen | *Do you consider ibrutinib 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)?*<br>Yes ibrutinib is truly innovative in its potential to make a significant and substantial impact on health-related benefits – please see detailed discussion on this point in response to "Innovation" in section "Comment 1: the draft scope". | Comments noted. No action required. |
| | Janssen | *Do you consider that the use of ibrutinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*<br>Yes - please see detailed discussion on this point in response to "Innovation" in section "Comment 1: the draft scope".<br>*Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits*.<br>The data available to enable the Appraisal Committee to take account of ibrutinib's benefits include long-term efficacy and safety data from a single-arm Phase 2 trial, from the pivotal randomised Phase 3 trial and from evidence generated through real-world data analysis. | Comments noted. No action required. |
| | Leukaemia CARE | No comments. | No action required. |

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| | Roche Products | No comments. | No action required. |
| Additional comments on the draft scope | | None. | |

**The following consultees/commentators indicated that they had no comments on the draft scope**

Department of Health, Napp Pharmaceuticals, Royal College of Nursing