**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Pirtobrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma [ID6397]**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-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.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Appropriateness of an evaluation and proposed evaluation route | CLL Support, Blood Cancer UK, Lymphoma Action, Leukaemia UK and Leukaemia Care (from now Joint Submission) | Appropriate | Thank you for your comment. No action required. |
| | The Royal College of Pathologists | The Royal College of Pathologists supports evaluation through a Single Technology Appraisal (STA). Pirtobrutinib is a novel non-covalent Bruton's tyrosine kinase (BTK) inhibitor and will enter an already established targeted treatment pathway in CLL/SLL. An STA is appropriate for focused assessment of clinical and cost effectiveness of a single agent within this pathway. | Thank you for your comment. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | UK CLL Forum | Pirtobrutinib has a marketing authorisation for the treatment of relapsed or refractory CLL who have been previously treated with a BTK inhibitor.<br>This current health technology evaluation is to assesses the clinical and cost effectiveness of pirtobrutinib for untreated patients with CLL and SLL<br><br>This is the appropriate pathway to assess this agent | Thank you for your comment. No action required. |
| | Eli Lilly | The company considers the single technology appraisal (STA) to be the most appropriate route for pirtobrutinib in untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), with a proportionate cost-comparison within the STA, subject to NICE's agreement on clinical comparability to at least one Bruton tyrosine kinase inhibitor (BTKi) already recommended for the same indication.<br>Bruton's tyrosine kinase (BTK) inhibition is an established and well-validated treatment strategy in untreated CLL, with multiple BTKi's currently recommended for use in this setting. These treatments share a common therapeutic intent: long-term disease control through continuous oral BTK inhibition.[1]<br>Pirtobrutinib targets the same BTK pathway and is intended for use in a clinically similar population to existing BTKis in BTKi-naïve CLL. Available evidence from the BRUIN-313/314 trials indicate that pirtobrutinib provides disease control consistent with that expected from other BTKis when used in BTKi-naïve patients. Pirtobrutinib is considered therapeutically comparable to established BTK inhibitors used in routine practice.[2,3]<br>The safety profile of pirtobrutinib is predictable and consistent with long-term oral BTKi therapy.[2,3] Consequently, no incremental non-drug costs are expected relative to current standard practice.<br>For this evaluation, pirtobrutinib should be compared with continuous BTKi therapies recommended by NICE for BTKi-naïve CLL/SLL, specifically | Thank you for your comment. Comment noted. This appraisal is being routed as an STA for which the reference case requires a cost-utility analysis. The company may submit additional scenarios exploring cost-comparison analyses. The committee will consider all analyses in its decision making. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | zanubrutinib (TA931). Acalabrutinib is also recommended (TA689); however, zanubrutinib is considered the most appropriate comparator for cost-comparison purposes given the strength of the SEQUOIA trial as an anchor.[4] More information on this is provided in the 'Comparators' section. | |
| | AbbVie | No Comment | Thank you for your comment. No action required. |
| | AstraZeneca | N/A | No action required. |
| | Johnson and Johnson Innovative Medicine | N/A | No action required. |
| Wording | Joint Submission | Yes | Thank you for your comment. No action required. |
| | The Royal College of Pathologists | The wording is broadly appropriate. However, treatment selection in CLL is genomically stratified in NHS practice. We suggest acknowledging this:<br><br>"To appraise the clinical and cost effectiveness of pirtobrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma, stratified by genomic risk factors including TP53 abnormality and IGHV mutation status."<br><br>CLL and SLL represent the same disease entity biologically, differing primarily by the degree of peripheral blood involvement. | Thank you for your comment. Comment noted. The committee are able to appraise subgroups of the population during the course of the appraisal (see subgroup section). |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | UK CLL Forum | Yes | Thank you for your comment. No action required. |
| | Eli Lilly | The remit is appropriate. | Thank you for your comment. No action required. |
| | AbbVie | No Comment | Thank you for your comment. No action required. |
| | AstraZeneca | N/A | No action required. |
| | Johnson and Johnson Innovative Medicine | N/A | No action required. |
| Timing Issues | Joint Submission | Urgent | Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required. |
| | The Royal College of Pathologists | There is moderate-to-high urgency. Although several effective targeted therapies exist, first-line CLL management is evolving rapidly and NICE | Thank you for your comment. Comments noted. NICE has scheduled this topic into |

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| | | guidance is needed to support consistent treatment sequencing and commissioning decisions. | its work programme. No action required. |
| | UK CLL Forum | We are fortunate that we have a number of options to treat patients with untreated CLL and SLL as outlined in the draft scope.<br><br>Pirtobrutinib in the front line setting would add a further treatment option for patients. It is unique in that it is a non-covalent BTK inhibitor (in comparison to Ibrutinib, Zanubrutinib and Acalabrutinib, which are all covalent inhibitors). Although there is evidence from a single randomised trial to demonstrate potential benefit vs Ibrutinib, this awaits confirmation with longer follow-up. There is no data of comparison of Pirtobrutinib vs the 2nd generation BTK inhibitors Acalabrutinib and Zanubrutinib.<br><br>The urgency of access of this agent in the front line setting is limited. | Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required. |
| | Eli Lilly | Targeted agents now represent the standard of care in first line treatment. Timely evaluation will help ensure patients have access to a full range of modern continuous therapies, furthermore, the cost-comparison route scheduling is appropriate. Timely evaluation will help ensure patients have access to a full range of continuous treatments. | Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required. |
| | AbbVie | No Comment | Thank you for your comment. No action required. |
| | AstraZeneca | N/A | No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Johnson and Johnson Innovative Medicine | N/A | No action required. |
| Additional comments on the draft remit | Joint Submission | None | Thank you for your comment. No action required. |
| | The Royal College of Pathologists | Therapy eligibility depends on laboratory testing (TP53 mutation, 17p deletion, IGHV mutation status). The remit should recognise the central role of pathology and genomic diagnostics in treatment selection. | Thank you for your comment. The role of diagnostics is addressed in the subgroup section of the scope. |
| | UK CLL Forum | N/A | No action required |
| | Eli Lilly | Not applicable. | No action required |
| | AbbVie | No Comment. | No action required |
| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |

Comment 2: the draft scope

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | Joint Submission | No comment | No action required |
| | The Royal College of Pathologists | Generally accurate. However, CLL management is now primarily molecularly stratified rather than stage-based. Diagnostic evaluation includes:<br><br>• flow cytometry immunophenotyping (CD5+/CD23+ B-cell population)<br>• FISH for 17p deletion<br>• TP53 mutation testing<br>• IGHV mutation analysis<br>• cytogenetic complexity assessment<br><br>These investigations directly determine treatment choice. | Thank you for your comment. Comment noted. The aim of the background is to provide a very brief summary of the disease area. Further details can be included in all submissions for this evaluation for consideration by the appraisal committee. |
| | UK CLL Forum | Appropriate<br><br>Comment: Venetoclax/Obinutuzumab should also be included in the options for no TP53 information, however this is appropriately included in the comparators below. | Thank you for your comment. The scope has been updated to reflect this. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Eli Lilly | The background currently cites earlier British Journal of Haematology guidance and should be updated to reflect the 2025 British Society for Haematology (BSH) Guideline for the treatment of CLL, which supersedes prior versions.[5] The 2025 BSH guideline:<br>• confirms that targeted agents have superseded chemo-immunotherapy, which is no longer routinely recommended except where targeted agents are unavailable or contraindicated<br>• recommends universal testing for *del(17p)/TP53* mutation and immunoglobulin heavy chain variable (*IGHV)* gene status to inform first-line choice<br>• lists continuous BTK inhibition (acalabrutinib or zanubrutinib) and fixed-duration venetoclax-based regimens (venetoclax-obinutuzumab or venetoclax-ibrutinib) as standard first-line options, using shared decision-making to select between fixed-duration and continuous approaches<br>The draft scope sentence suggesting targeted therapies are "particularly useful" only in high-risk disease should be revised, as targeted agents now constitute standard of care across risk groups | Thank you for your comment. Comment noted. The scope has been updated with suggested wording to reflect targeted therapies. |
| | AbbVie | AbbVie would like the following change to be made per the notation (yellow highlighting denotes where wording has been added in) below, given that targeted therapies are reimbursed on a wider basis including those patients with poor prognosis, additionally fixed treatment durations in 1L CLL do not have scheduled breaks:<br><br>*'Targeted therapies such as zanubrutinib, acalabrutinib, ibrutinib, and venetoclax are often the first choice of treatment. ~~Targeted therapies, such as zanubrutinib, acalabrutinib, ibrutinib, and venetoclax are particularly useful in people with a poor prognosis, such as those with 17p deletion or TP53~~* | Thank you for your comment. As the background section is only intended to give a brief overview of the disease area, because the comparators are listed in the PICO table and for simplicity Table 1 has now been deleted. |

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| | | *~~mutation.~~ Treatments may be for a fixed duration (also called time-limited) ~~with scheduled treatment breaks,~~ or continuous therapy for as long as appropriate.'*<br><br>Table 1 of the background section presents the comparators in a confusing manner and could easily lead to a misinterpretation of the AbbVie would like the following change to be made per the notation (yellow highlighting denotes where wording has been added in) below, given that targeted therapies are reimbursed on a wider basis including those patients with poor prognosis, additionally fixed treatment durations in 1L CLL do not have scheduled breaks:<br><br>'Targeted therapies such as zanubrutinib, acalabrutinib, ibrutinib, and venetoclax are often the first choice of treatment. Targeted therapies, such as zanubrutinib, acalabrutinib, ibrutinib, and venetoclax are particularly useful in people with a poor prognosis, such as those with 17p deletion or TP53 mutation. Treatments may be for a fixed duration (also called time-limited) with scheduled treatment breaks, or continuous therapy for as long as appropriate.'<br><br>Table 1 of the background section presents the comparators in a confusing manner and could easily lead to a misinterpretation of the reimbursement of the different therapies. For example:<br>- It is unclear which mutation is being referenced in the subheading 'for adults with untreated CLL where mutation is not specified.' Is this referencing IGHV mutation or 17p deletion or TP53 mutation?<br>- Given the new NICE guidance (TA1119), AbbVie believe venetoclax with obinutuzumab should be shown in the same bucket as ibrutinib with venetoclax. The NICE guidance for both states they are options 'for untreated chronic lymphocytic leukaemia (CLL) in adults.'<br>- The table seems to suggest broad reimbursement for both zanubrutinib and acalabrutinib, however, this is not the case and is spoken about in the comparators section below. | |

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| | | AbbVie would suggest that this table is simplified to ensure people can easily understand the reimbursement criteria. For example:<br>- Adults with untreated CLL with a 17p deletion or TP53 mutation: Acalabrutinib, Zanubrutinib, Venetoclax, Ibrutinib with Venetoclax, Venetoclax with Obinutuzumab<br>- Adults with untreated CLL without 17p deletion or TP53 mutation: Acalabrutinib (where fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR) is unsuitable), Zanubrutinib (where FCR/BR are unsuitable), Ibrutinib with Venetoclax, Venetoclax with Obinutuzumab | |
| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |
| Population | Joint Submission | Yes – an unrestricted patient population | Thank you for your comment. No action required. |
| | The Royal College of Pathologists | Appropriate.<br>However, not all newly diagnosed patients require treatment. Therapy is initiated only when patients meet iwCLL treatment criteria; many remain on active surveillance for prolonged periods.<br><br>CLL and SLL should both be included, as they are managed identically. | Thank you for your comment. Comment noted. No action required. |

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| | UK CLL Forum | Appropriate | Thank you for your comment. No action required. |
| | Eli Lilly | The population is not defined appropriately and is wider than that stated within the scope. The population should be defined as:<br>"Adults with CLL or small lymphocytic leukaemia that are BTKi-treatment naïve". | Thank you for your comment. The scope has been updated with the suggested wording. |
| | AbbVie | No Comment | Thank you for your comment. No action required |
| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |
| Subgroups | Joint Submission | Subgroups have been suggested and appear appropriate for consideration if necessary.<br>We would suggest an additional population – the elderly may find this treatment more tolerable than the covalent BTKi's<br>The importance of suitability of use with poor renal function is important. | Thank you for your comment. Comment noted. As age is a protected characteristic it is not usually included as a subgroup. However, the company will have the opportunity to justify any exclusion of these |

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| | | | subgroups or inclusion of additional subgroups in their submission. |
| | The Royal College of Pathologists | Appropriate and clinically important:<br>• TP53 mutation/17p deletion<br>• IGHV mutation status<br>• complex karyotype<br>We additionally suggest including: patients unsuitable for covalent BTK inhibitors (e.g., cardiovascular comorbidity, high bleeding risk or intolerance). | Thank you for your comment. The scope has been updated to reflect this. |
| | UK CLL Forum | Based on the trial information we have available no subgroup specific recommendations can be made.<br><br>Based on some the clinical trial data available, Pirtobrutinib has been compared with Bendamustine/Rituximab chemoimmunotherapy. In this study TP53 mutated patients were included but patients with 17p deletion are excluded. Further, evaluation of cost-effectiveness is likely to require indirect comparisons, given the comparator arm of the trial is no longer in use. Inclusion/exclusion of these patients with TP53 mutations in the indirect comparisons only will have to be carefully considered.<br><br>Ideally, as stakeholders we would prefer a separate analysis of TP53 intact and mutated/deleted patients, assessing cost-effectiveness separately for these two groups. | Thank you for your comment. Comment noted. No action required. |

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| | Eli Lilly | Reimbursement is being sought for the intention-to-treat population of the BRUIN-313 and BRUIN-314 trials.[2,3] | Thank you for your comment. No action required. |
| | AbbVie | No Comment | Thank you for your comment. No action required. |
| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |
| Comparators | Joint Submission | Yes | Thank you for your comment. No action required. |
| | The Royal College of Pathologists | Appropriate and reflective of NHS practice.<br><br>However, modelling should consider treatment pathways/strategies (continuous BTK inhibition vs fixed-duration venetoclax-based therapy) rather than single drugs alone, as this reflects real clinical decision-making.<br><br>Note: Chemo-immunotherapy (for example FCR and bendamustine-rituximab) is now used infrequently but may still be considered in selected patients (such as younger/fit patients with IGHV-mutated disease and no TP53 abnormality) or where targeted therapies are contraindicated. NICE may therefore wish to consider whether inclusion as secondary comparators is appropriate to reflect residual NHS use. | Thank you for your comment. Comment noted. The company may choose to include/exclude comparators from its submission but should provide clear justification for doing so. |

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| | UK CLL Forum | Yes, including the potential use of Acalabrutinib and Venetoclax fixed duration treatment. | Thank you for your comment. Comment noted. No action required |
| | Eli Lilly | Pirtobrutinib is positioned as a treatment for patients who are BTKi treatment naïve. The introduction of pirtobrutinib will not change the clinical decision regarding whether a patient should begin treatment with a BTKi or a *BCL2* inhibitor (BCL2i) regimen. Patients considered suitable for treatment with pirtobrutinib would not be considered appropriate candidates for fixed-duration therapies.[5] Subsequently, the relevant standard of care for this population is continuous treatment with established an established BTKi monotherapy.<br>The primary comparator is zanubrutinib, because it is a NICE-recommended, routinely commissioned continuous BTKi for first-line CLL (TA931) and its recommendation is underpinned by SEQUOIA (randomised zanubrutinib versus bendamustine-rituximab). [4] BRUIN-313 for pirtobrutinib also uses bendamustine-rituximab, providing a robust anchor and reinforcing the choice of zanubrutinib for a proportionate within-class comparison. Both drugs share the same therapeutic intent and care model (continuous oral BTK inhibition).[2,4]<br>Use of one justified comparator aligns with NICE's cost-comparison route, which requires demonstrating clinical similarity to at least one previously recommended treatment option.<br>Acalabrutinib remains a valid comparator, but to keep the appraisal proportionate it will not be included in the base case; zanubrutinib will serve as the single cost-comparison comparator. | The comparator list has been kept inclusive at this stage to allow committee to consider all potential comparators. This appraisal is being routed as an STA and the NICE reference case specifies cost-utility modelling. The company are free to submit additional scenarios exploring cost-comparison analyses. The committee will consider all presented analyse and scoped comparators. |
| | AbbVie | It is important to explicitly state in the final appraisal scope that reimbursement for: | Thank you for your comment. The scoped comparators cover any treatment which might |

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| | | - Zanubrutinib and Acalabrutinib in first-line CLL is limited to patients deemed unsuitable for treatment with FCR/BR.<br>- Venetoclax monotherapy is recommended for patients with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable<br>- Ibrutinib is recommended for patients who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable<br><br>For context, the new British Society of Haematology (BSH) guidelines (2025), linked here, move away from suitability for FCR and BR (as relevant for Zanubrutinib and acalabrutinib), however the clarification above will ensure accurate representation of the current NICE recommended wording pending a NICE review of all CLL guidance wording. | be considered a comparator. This can include treatments used off-label or outside of a NICE recommendation if they are established in clinical practice. The comparators list has been kept inclusive at this stage to allow all potential comparators to be considered by committee. Mutation status is covered in the subgroups section. |
| | AstraZeneca | During the scoping consultation for ID6232, Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia (AV/AVO), the company (AstraZeneca UK) highlighted the extensive list of comparators included in the draft scope. These included treatments which were not relevant in clinical practice anymore, such as obinutuzumab with chlorambucil (O-Clb), rituximab with fludarabine and cyclophosphamide (FCR), bendamustine, and bendamustine with rituximab (BR). As such, and based on treatment guidelines and feedback from UK clinical experts, AstraZeneca UK requested that NICE revise the scope to only include comparators that are relevant in clinical practice.<br><br>NICE at the time decided to retain the full list of comparators as “those listed in the scope are intended to be broad”. As such, the final scope for ID6232 | Thank you for your comment. The comparators have been updated in line with all consultation comments and the BSH guideline to try to best reflect the targeted options which may be used in clinical practice. The Committee will consider which comparators are relevant during the appraisal. |

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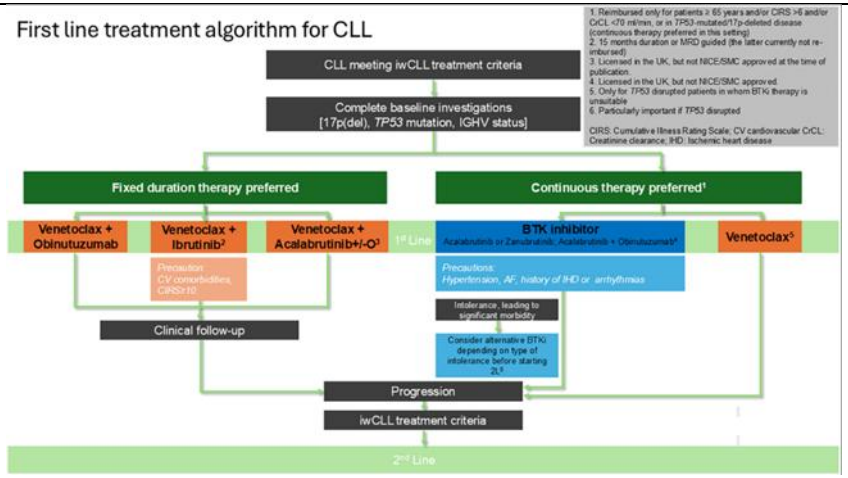
| | | includes a broad list of comparators, most of which are not relevant in current clinical practice in the UK.<br><br>Since ID6397 addresses in part a similar population to that in ID6232 (i.e. first line CLL), the comparators are expected to be as broad and comprehensive. NICE suggests that a strong and clear rationale should be provided for excluding any comparators from the evidence submission and that these would be discussed with the committee for a decision to be made.<br><br>For consistency and completeness, we request that the comparators list in the scope for ID6397 to be equally broad to that in ID6232. | |
| | Johnson and Johnson Innovative Medicine | Our view is that Ibrutinib + Venetoclax does not represent an appropriate comparator.<br>Recently published BSH guidelines for front line CLL ,leads with a choice between continuous treatment vs fixed duration treatments. the choice is made in consultation with the patient and takes into account several factors including but not limited to disease biology, toxicity, concomitant medications, practicality and desire for treatment free intervals. | Thank you for your comment. The scoped comparators to try to best reflect the targeted options which may be used in clinical practice. The Committee will consider which comparators are relevant during the appraisal. |




Pirtobrutinib was studied in the BRUIN CLL-313 as a continuous mono-therapy treatment option. As such, it would be more appropriate for it to be compared to other licensed/NICE recommended continuous treatment options. Ibrutinib as monotherapy has the longest and most robust PFS and OS data (RCT - PCYC-1115-CA) of any of the licensed BTKi continuous treatment options and would be more appropriate as a comparator for this appraisal as comparted to I+V which had a fixed duration of 15 months ibrutinib combined for the last 12 months with Venetoclax.

Reference:

Walewska R, Eyre TA, Bloor A, Follows G, Iyengar S, Johnston R, et al. 2025 British Society for Haematology Guideline for the treatment of chronic lymphocytic leukaemia. Br J Haematol. 2025; 207(6): 2296–2313. https://doi.org/10.1111/bjh.70100

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| Outcomes | Joint Submission | Yes, a comprehensive list of outcome measures have been listed including MRD status, time to treatment failure and adverse events. | Thank you for your comment. Comment noted. No action required. |
| | The Royal College of Pathologists | Appropriate but could additionally include:<br>• treatment discontinuation due to intolerance<br>• cardiovascular toxicity (e.g. atrial fibrillation)<br>• infection-related hospitalisation<br>• treatment-free remission duration<br>MRD is useful but should not be treated as a validated survival surrogate across all therapies. | Thank you for your comment. Comment noted. No action required. |
| | UK CLL Forum | Yes | Thank you for your comment. Comment noted. No action required. |
| | Eli Lilly | The outcomes listed are appropriate. | Thank you for your comment. Comment noted. No action required. |
| | AbbVie | No Comment | No action required |
| | AstraZeneca | N/A | No action required |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Johnson and Johnson Innovative Medicine | N/A | No action required |
| Equality | Joint Submission | No equality issues | Thank you for your comment. Comment noted. No action required. |
| | The Royal College of Pathologists | No intrinsic equality issues identified.<br>However, access to molecular testing must be equitable across geographical regions. Availability of prognostic marker testing (FISH, sequencing, IGHV analysis) is essential to avoid unequal treatment access. | Thank you for your comment. Comment noted. No action required. |
| | UK CLL Forum | No concerns in relation to equality impact | Thank you for your comment. Comment noted. No action required. |
| | Eli Lilly | The company has not identified any wording that risks excluding protected groups. | Thank you for your comment. Comment noted. No action required |
| | AbbVie | No Comment | Thank you for your comment. Comment noted. No action required |

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| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |
| Other considerations | Joint Submission | None | Thank you for your comment. No action required. |
| | The Royal College of Pathologists | The evaluation should consider pathology resource impact, including baseline testing (flow cytometry, FISH, TP53 sequencing, IGHV analysis, cytogenetics) and monitoring such as MRD assessment. | Thank you for your comment. No action required. |
| | UK CLL Forum | NA | No action required. |
| | Eli Lilly | Not applicable. | No action required |
| | AbbVie | No Comment | No action required |
| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |

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| Questions for consultation | Joint Submission | **Where do you consider pirtobrutinib will fit into the existing care pathway for chronic lymphocytic leukaemia or small lymphocytic lymphoma?**<br>For this TA Pirtobrutinib will be an option for first line treatment of CLL/SLL<br>**Have all relevant comparators been included in the draft scope?**<br>Yes, it's noted that AVO is also included which does not have NICE TA recommendation at the current time.<br>**Which of the listed comparators would pirtobrutinib be most likely to displace if it were recommended?**<br>Pirtobrutinib is likely to displace venetoclax + obintuzumab and Venetoclax monotherapy for patients with significant renal disease who may have difficulties completing the dosage ramp up safely.<br>It may replace covalent BTKi's for the elderly or those with some comorbidities as the incidence of cardiovascular AEs is reported as very low relative to the current first line BTKi's.<br>**Could you estimate what proportions of people with untreated CLL have the listed comparators in NHS clinical practice?**<br>As a patient group we are unable to answer this question.<br>**Have all relevant subgroups been included in the draft scope?**<br>Yes, however, consideration could be given for those with severe renal disease if<br>**What is the distinction between chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL)? Does the anticipated marketing authorisation for pirtobrutinib for this appraisal cover SLL?**<br>We anticipate that the expected marketing authorisation will include SLL. | Thank you for your comment. Comments noted. No action required. |

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| | | **Is the clinical trial evidence that could inform this evaluation generalisable to the NHS clinical practice population? If not, could you explain why?**<br>Yes<br><br>**We expect that Pirtobrutinib will be prescribed in secondary care with routine follow-up also in secondary care**<br><br>**For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.**<br>We expect comparators and subsequent treatments will also be prescribed in secondary care with routine follow-up in secondary care<br>**Would Pirtobrutinib be a candidate for managed access?**<br>Yes, if the committee feels there is insufficient evidence at this time to approve Pirtobrutinib for untreated CLL we feel that managed access is an excellent route allow patient's access to the treatment and real-world evidence to be gathered over a limited time period, managed by NICE.<br>**Do you consider that the use of pirtobrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br>**Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits**.<br>Pirtobrutinib may offer substantial health-related benefits that are not fully captured in QALY estimates, particularly in untreated CLL/SLL. As a highly selective non-covalent BTK inhibitor, it may be associated with improved tolerability and a lower burden of clinically significant adverse events, leading to sustained quality of life over long treatment durations, reduced treatment burden, and fewer disruptions to daily living, which are not well reflected in EQ-5D. | |

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| | | Additional benefits may include reduced healthcare resource use, greater convenience associated with oral administration, and potential option value through preservation of future treatment choices in a chronic, relapsing condition – opening subsequent lines of treatment.<br>Evidence to support consideration of these benefits may include patient-reported outcome data (e.g. EORTC QLQ-C30, FACIT-Fatigue – these are not all freely accessible so I have not seen all these sets), safety and tolerability data from clinical trials (e.g. BRUIN CLL-313 - Phase 3 / BRUIN CLL-314 - Phase 3 / BRUIN Phase 1/2 Study), healthcare resource use data, time-to-next-treatment outcomes, real-world evidence, and qualitative patient and carer submissions.<br><br>**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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope**:<br><br>• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pirtobrutinib will be licensed;<br><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;<br><br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. | |

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| | | No comment | |

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| | The Royal College of Pathologists | **Position in care pathway**<br>Pirtobrutinib would most likely enter first-line treatment as an alternative BTK-pathway therapy, particularly for patients unsuitable for covalent BTK inhibitors or requiring improved tolerability.<br><br>**Comparators included**<br>Yes.<br><br>**Comparator most likely displaced**<br>Covalent BTK inhibitors (acalabrutinib, zanubrutinib, and ibrutinib-containing strategies).<br><br>**Proportion of patients receiving comparators**<br>Exact utilisation data is not held by the College. In current NHS practice both BTK inhibitor strategies and venetoclax-based regimens are commonly used, with local variation based on comorbidity and molecular risk.<br><br>**Subgroups**<br>Relevant subgroups are included, but BTK-intolerant patients should be considered.<br><br>**CLL vs SLL**<br>CLL and SLL are the same disease entity; diagnosis depends on whether lymphocytosis ≥5 × $10^9$/L is present in peripheral blood. Both share identical immunophenotypic and molecular features and are treated identically. | Thank you for your comment. Comments noted. No action required. |

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| | | **Generalisability**<br>Trial populations are broadly representative but may under-represent frail elderly patients and those with significant comorbidity commonly seen in NHS practice.<br><br>**Prescribing setting**<br><br>Secondary care prescribing and follow-up.<br><br>**Comparator setting**<br><br>Same as intervention.<br><br>**Managed access**<br><br>Potentially appropriate given evolving sequencing questions and immature long-term outcome data.<br><br>**Health benefits not captured in QALY**<br><br>Possible benefits include improved tolerability and reduced cardiovascular toxicity compared with covalent BTK inhibitors, which may improve adherence and treatment persistence.<br><br>**Data sources**<br><br>Clinical trial data (e.g. BRUIN programme), safety data, patient-reported outcomes, and real-world evidence registries. | |
| | UK CLL Forum | N/A | No action required |

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| | Eli Lilly | **Where do you consider pirtobrutinib will fit into the existing care pathway for CLL or SLL?**<br>Pirtobrutinib is intended as an alternative continuous BTKi for people who are BTKi-naïve, for whom continuous BTKi therapy is preferred over a fixed-duration *BCL2*i-based approach. This is consistent with current UK practice in which clinicians select between these two treatment paradigms based on individualised choice.[5]<br>**Have all relevant comparators been included in the draft scope?**<br>Yes, the relevant BTKis (zanubrutinib and acalabrutinib), are included in the draft scope.<br>**Which of the listed comparators would pirtobrutinib be most likely to displace if it were recommended?**<br>The company anticipates that pirtobrutinib would be considered among the options for patients for whom continuous BTKi therapy is appropriate. Its introduction is not expected to replace existing therapies but rather to share usage within the current BTKi treatment landscape.<br>**Could you estimate what proportions of people with untreated CLL have the listed comparators in NHS clinical practice?**<br>Most CLL drugs are high-cost hospital medicines; publicly available NHS usage data does not provide accurate indication or line-specific volumes for CLL, making reliable market-share estimation difficult without proprietary data. The company intends to explore this prior to submission.<br>**Have all relevant subgroups been included in the draft scope?**<br>Yes.<br>**What is the distinction between CLL and SLL? Does the anticipated marketing authorisation for pirtobrutinib for this appraisal cover SLL**?<br>CLL and SLL are considered a single biologic entity and following diagnosis patients are considered as a single patient group and receive the same treatment. The abnormal B cells are indistinguishable between the two diseases with the only distinction being that the accumulation of abnormal B | Thank you for your comment. Comments noted. No action required. |

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| | | cells occurs in the blood and bone marrow in CLL and in the lymph nodes in SLL.[6]<br>**Is the clinical trial evidence that could inform this evaluation generalisable to the NHS clinical practice population? If not, could you explain why?**<br>The clinical trial evidence is generalisable to the NHS clinical practice population. The BRUIN studies are large, global, multicentre, studies that include UK sites and enrolled a representative CLL/SLL population. There are no generalisability concerns.[2,3]<br>**Please select from the following, will pirtobrutinib be:**<br>• ~~Prescribed in primary care with routine follow-up in primary care~~<br>• ~~Prescribed in secondary care with routine follow-up in primary care~~<br>• Prescribed in secondary care with routine follow-up in secondary care<br>• ~~Other (please give details):~~<br>**For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.**<br>This prescribing and routine follow-up setting mirrors that of currently used BTKis.<br>**Would pirtobrutinib be a candidate for managed access?**<br>The company does not anticipate that a managed access route would be necessary for pirtobrutinib.<br>**Do you consider that the use of pirtobrutinib can result in any potential substantial health related benefits that are unlikely to be included in the QALY calculation?**<br>Not applicable to the cost-comparison route | |

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| | | 1. Tam C, Thompson PA. BTK inhibitors in CLL: second-generation drugs and beyond. *Blood Advances*. 2024;8(9):2300-2309. doi:10.1182/bloodadvances.2023012221<br>2. Eli Lilly and Company. BRUIN-313 Clinical Study Report. *Data on File,*. 2025;<br>3. Eli Lilly and Company. BRUIN-314 Clinical Study Report. *Data on File,*. 2025;<br>4. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *The Lancet Oncology*. 2022;23(8):1031-1043. doi:10.1016/S1470-2045(22)00293-5<br>5. Walewska R, Eyre TA, Bloor A, et al. 2025 British Society for Haematology Guideline for the treatment of chronic lymphocytic leukaemia. *British Journal of Haematology*. 2025/12/01 2025;207(6):2296-2313. doi:10.1111/bjh.70100<br>6. Lymphoma Action. Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL). Updated April 2023. Accessed 10 February, 2026. https://lymphoma-action.org.uk/information-and-support/types-lymphoma/chronic-lymphocytic-leukaemia-cll-and-small-lymphocytic#what-is | |
| | AbbVie | No Comment | No action required. |
| | AstraZeneca | N/A | No action required. |
| | Johnson and Johnson | N/A | No action required. |

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| | Innovative Medicine | | |
| Additional comments on the draft scope | Joint Submission | **Bruin CLL 314 trial: Pirtobrutinib v Ibrutinib**<br>• Among treatment-naive and BTKi-naive patients with CLL/SLL, pirtobrutinib demonstrated noninferior ORR vs ibrutinib in the ITT and R/R populations<br>• Pirtobrutinib appeared to be associated with increased PFS in ITT, treatment-naive, and R/R populations in early analysis<br>• Pirtobrutinib was effective in treatment-naive patients, with an ORR of 92.9% vs 85.8%; PFS benefit vs ibrutinib: HR 0.239 (95% CI: 0.098-0.586); *P* = .0007<br>• Investigators conclude that pirtobrutinib was effective and generally well tolerated in this CLL/SLL patient population, with low discontinuation rates and few occurrences of atrial fibrillation/flutter, in particular among patients aged ≥75 yr which may make it a better option for elderly patients with cardiovascular comorbidities.<br>**CLL313 Trial Pirtobrutinib v Bendamustine +Rituximab**<br>• Pirtobrutinib demonstrated superiority over BendaR in IRC-assessed PFS in treatment-naïve CLL/SLL. | Thank you for your comment. Comment noted. No action required. |
| | The Royal College of Pathologists | N/A | Thank you for your comment. No action required. |
| | UK CLL Forum | No additional comments. | No action required. |

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| | Eli Lilly | NA | No action required. |
| | AbbVie | In the technology section of the draft scope only one of the two clinical trials is mentioned. For completeness AbbVie believe both should be mentioned:<br>- BRUIN CLL-313: Randomized Phase III Trial of Pirtobrutinib Versus Bendamustine Plus Rituximab in Untreated Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma<br>- BRUIN CLL-314: A Phase III Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) Versus Ibrutinib in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma<br>Within the NICE Related technology appraisals in development section, venetoclax with obinutuzumab appears, however, this indication is now routinely reimbursed and published on the NICE website. AbbVie believe this should be moved to the section above i.e. related NICE recommendations and should be amalgamated with Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (2020). NICE technology appraisal guidance 663. Review date 2023, to be Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (2026). NICE technology appraisal guidance 1119. | Thank you for your comment. Comment noted. No action required. |
| | AstraZeneca | N/A | No action required |
| | Johnson and Johnson Innovative Medicine | N/A | No action required |

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

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