National Institute for Health and Care Excellence

Health Technology Evaluation

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]
Response to stakeholder organisation 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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	BeiGene UK	It is appropriate to refer zanubrutinib to NICE for appraisal.	Thank you for your comment. No action needed.
	UK CLL FORUM	**Relapsed or refractory** Bruton tyrosine kinase (BTK) inhibitors, BCL2 inhibitors and combinations thereof are currently the cornerstone of CLL management. Zanubrutinib has been developed with the intention of minimising off-target adverse effects, which continue to limit the use of its predecessor ibrutinib. The ALPINE study directly compares the use of zanubrutinib and ibrutinib in relapsed or refractory CLL. **Untreated** Bruton tyrosine kinase (BTK) inhibitors, BCL2 inhibitors and combinations thereof are currently the cornerstone of CLL management. Zanubrutinib has	Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
		been developed with the intention of minimising off-target adverse effects, which continue to limit the use of its predecessor ibrutinib. The SEQUOIA study does not directly compare zanubrutinib with another BTK inhibitor, but provides important information on its efficacy and side effects in the upfront setting.	
Wording	BeiGene UK	The wording of the draft remit reflects the issue of clinical and cost-effectiveness about zanubrutinib and is aligned with both the anticipated marketing authorisation and use of zanubrutinib within clinical practice in England and Wales.	Thank you for your comment. No action needed.
	UK CLL FORUM	Wording of the Draft remit/evaluation objective is fine	Thank you for your comment. No action needed.
Timing issues	BeiGene UK	This appraisal should be initiated as soon as possible. As reported in 'Appendix B – Draft scope ID5078' and 'Appendix B - Draft scope ID5079', around 3,800 people are diagnosed with chronic lymphocytic leukaemia (CLL) in the United Kingdom (UK) each year. People with untreated CLL live with a considerable burden of symptoms impacting their quality of life.[1] Following an initial response to treatment, most patients with CLL relapse and need additional therapy. In addition, a proportion of patients have disease which is refractory to initial treatment.[1] Treatment of CLL is complex and depends on several factors such as stage of disease, previous treatment, patient's age, symptoms, and general state of health. A choice of treatment options is vitally important for patients with CLL, both due to the heterogeneity of the disease but also because the comorbidities that are often present in the older population mean that not all treatments are suitable for every patient.	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
		Targeted therapies have been shown to improve outcomes for patients, particularly those with a poor prognosis, such as older patients, patients with comorbidities, patients with 17p deletion or TP53 mutation, and patients with relapsed or refractory disease. During the SEQUOIA trial, a phase 3 study for patients with untreated CLL, zanubrutinib demonstrated significantly improved progression-free survival versus bendamustine-rituximab.[2] Zanubrutinib was generally well-tolerated, consistent with its known safety profile in Waldenstrom's macroglobulinemia (WM) and its design to minimise off-target inhibition and hence toxicity.[3–5] During the ALPINE trial, a phase 3 study for patients with relapsed or refractory CLL, zanubrutinib demonstrated superior therapeutic value to ibrutinib during the interim readout.6 Zanubrutinib demonstrated an improved safety profile compared to ibrutinib, demonstrating a statistically significant lower risk of atrial fibrillation or flutter and advantages in the overall cardiac safety profile.[6] The introduction of zanubrutinib into the treatment paradigm increases patient and clinician choice by providing an effective and tolerable next-generation Bruton tyrosine kinase inhibitor (BTKi) treatment option. References 1. National Health Service. Overview Chronic lymphocytic leukaemia [Internet]. 2019 [cited 2022 Aug 25]. Available from: https://www.nhs.uk/conditions/chronic-lymphocytic-leukaemia/ 2. Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a	

Section	Stakeholder	Comments [sic]	Action
		randomised, controlled, phase 3 trial. The Lancet Oncology. 2022;23(8):1031–43. 3. Helwick C. Zanubrutinib Superior to Ibrutinib for CLL/SLL in Phase III ALPINE Trial. Supplement: Hematologic Oncology Almanac Get Permission. 2022; 4. National Institute for Health and Care Excellence E. Zanubrutinib for Waldenström's macroglobulinaemia [Internet]. 2022 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/gid-ta10705/documents/1 5. Tam CS, Dimopoulos M, Garcia-Sanz R, Trotman J, Opat S, Roberts AW, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. Blood advances. 2022;6(4):1296–308. 6. Hillmen P, Eichhorst B, Brown J, Lamanna N, O'Brien S, Tam C, et al. First Interim Analysis of ALPINE Study: results of a Phase 3 Randomised Study of Zanubrutinib versus Ibrutinib in Patients with Relapsed/ Refractory Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma. British journal of haematology. 2022;197(SUPPL 1):92-93.	
	Leukaemia Care	**<u>Untreated CLL</u>** There are fewer option of BTK inhibitors available to those who are untreated compared to those relapsed. There is a need to ensure as many options are available to people upfront to allow better shared decision making and give clinicians more freedom to personalise medicines.	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
	UK CLL FORUM	**Relapsed or refractory CLL** The BTK inhibitors ibrutinib and acalabrutinib are already available to this patient group but this drug may offer a better side effect profile or be more cost effective. **Untreated CLL** The BTK inhibitor acalabrutinib is already available patient with co-morbidities via Blueteq, a similar cohort to the patients considered in the SEQUOIA study. Zanubrutinib may, however, offer a better side effect profile or be more cost effective.	Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BeiGene UK	The Company agrees that the background information gives a reasonable summary of clinical practice for CLL. However, it should be noted that since 2018, the introduction of targeted pathway inhibitors, in the form of BTKi or B-cell lymphoma 2 inhibitors (BCL2i), has represented a paradigm shift in the treatment of CLL and have challenged the role of chemo-immunotherapy. As described in the 2022 BSH guidelines, bendamustine-based, and chlorambucil-based chemo-immunotherapy regimens are no longer recommended for treating both untreated and relapsed/refractory CLL.[7] Feedback received from five UK clinicians, gathered in double-blinded 1:1 interviews conducted by the Company, confirmed that the use of chemo-immunotherapy was limited in clinical practice due to the availability of novel	Thank you for your comment. The scope has been updated to reflect this.

Section	Consultee/ Commentator	Comments [sic]	Action
		targeted therapies which offer improved efficacy, less toxicity, and convenience of administration without the need for hospital visits.[8] Whilst the choice of front-line treatment is driven by patients' mutational status and fitness level, the 2022 BSH guidelines recommend a 'sequencing' approach when selecting the optimal strategy for patients relapsing following treatment with front-line targeted agents. For patients progressing following front-line treatment with a BTKi, a BCL2i regimen is recommended and for patients progressing following front-line treatment with a BCL2i, a BTKi regimen is recommended.[7] Feedback received from five UK clinicians, gathered in double-blinded 1:1 interviews conducted by the Company, confirmed that a 'sequencing' approach is widely used when selecting a second-line treatment option.[8] The 2022 BSH guidelines suggest either idelalisib-rituximab or treatment within a clinical trial as a last-line treatment option for patients unsuitable for or who are refractory to BTKi- and BCL2i-based treatment, further highlighting that chemo-immunotherapy is no longer standard of care.[7] As such, a number of treatments listed in Table 1 of 'Appendix B - Draft scope ID5078' and Table 1 of 'Appendix B - Draft scope ID5079' should no longer be considered relevant comparators for zanubrutinib as described in the comparators section below. 7. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology. 2022;197(5):544–57.	

Section	Consultee/ Commentator	Comments [sic]	Action
		8. BeiGene. Data on file. 2022;	
	UK CLL FORUM	**Have made some alterations:** CLL is a blood cancer characterised by overproduction of lymphocytes which a sub-type of white blood cells. These cells are made in the bone marrow and are clonally identical, but they do not develop fully and as a consequence of this immaturity, don't function normally. The disease usually progresses slowly, but over time, patients can develop anaemia, swollen lymph nodes, splenic enlargement and unexplained weight loss. People with CLL may live with a considerable burden of symptoms and an increased susceptibility to infection1 impacting on their quality of life, whether or not they have received treatment. The British Society of Haematology (BSH) defines people with 'high risk' CLL as those with previously untreated CLL associated with a 17p deletion or TP53 mutation. The presence of a 17p deletion or TP53 mutation is associated with a poorer prognosis and resistance to conventional chemotherapy agents4. Many people with CLL will not have symptoms when they first receive a diagnosis and will have a period of active surveillance, They are monitored for progression of their disease and treatment is initiated according to criteria set out in international guidelines. CLL is not curable but with treatment the disease enters a period of remission before any further treatment is required. Abnormalities of the p53 gene and the mutational status of the immunoglobulin heavy chain gene (IgHV) mutation affect clinical outcomes5. We also have increasing knowledge of a range of other cytogenetic and	Thank you for your comment. The scope has been updated to reflect this.

Section	Consultee/ Commentator	Comments [sic]	Action
		molecular abnormalities within an individual's CLL cells which can affect both the clinical course of the disease and its response to treatment. The advent of targeted agents which are both more gentle and efficacious extends the benefits of active treatment to frailer patients and leads to more durable remissions. These newer drugs also largely overcome chemotherapy resistance in patients with 17p deletion or TP53 mutation. Next-generation BTK inhibitors such as zanubrutinib have improved selectivity and therefore less off-target side effects which is potentially of huge benefit to all CLL patients.	
Population	BeiGene UK	[redacted]	Thank you for your comment. The 2 scopes have been combined into 1 evaluation. The scope has been updated to reflect this.
	UK CLL FORUM	Accurate	Thank you for your comment. No action needed.
Subgroups	BeiGene UK	**<u>Relapsed or refractory CLL</u>** The following subgroups suggested in the scope are not considered appropriate for the appraisal of zanubrutinib for relapsed or refractory CLL: • People with a 17p deletion or TP53 mutation • According to immunoglobulin heavy chain (IgHV) mutation status (mutated or unmutated) As a 'sequencing' approach is recommended in the 2022 BSH guidelines when selecting the optimal strategy for patients who have relapsed following	Thank you for your comment. The subgroups have been updated to remove IgHV mutation status.

Section	Consultee/ Commentator	Comments [sic]	Action
		treatment with front-line targeted agents, treatment decisions for second-line treatments and beyond are made irrespective of 17p deletion, TP53 or IgHV mutation status. As such, these subgroups are considered inappropriate.[7] In addition, the 2022 BSH guidelines state that it is unclear whether IgHV status should be used to determine the use of BTKi- or BCL2i-based treatment.[7] As such, there is no clear benefit to considering patients according to IgHV mutation status. Furthermore, in the ALPINE trial, no significant difference in the treatment effect of zanubrutinib across the IgHV subgroups (mutated and unmutated) was observed for progression-free survival and overall response rate.[6] As such, no differences in the clinical effectiveness and cost-effectiveness of zanubrutinib is anticipated across these subgroups. Finally, the NICE recommendations for other relevant BTKis (acalabrutinib [TA689][10] and ibrutinib [TA429][9]) for patients with relapsed/refractory CLL did not include specification on subgroups by IgHV mutation status or 17p deletion/TP53 mutation, further highlighting that treatment decisions in this patient population is made irrespective of subgroups. Therefore, it is not considered appropriate to subgroup patients within the appraisal of zanubrutinib in patients with relapsed or refractory CLL and these subgroups should be removed from 'Appendix B - Draft scope ID5078'. **<u>Untreated CLL</u>** The following subgroups suggested in the scope are not considered appropriate for the appraisal of zanubrutinib for untreated CLL:	Thank you for your comment. The

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		• According to IgHV mutation status (mutated or unmutated) The 2022 BSH guidelines state that it is unclear whether IgHV status should be used to determine the use of BTKi- or BCL2i-based treatment.[7] As such, there is no clear benefit to considering patients according to IgHV mutation status. Furthermore, in the SEQUOIA trial, no significant difference in the treatment effect of zanubrutinib across the IgHV subgroups (mutated and unmutated) was observed for progression-free survival.[2] Furthermore, previous NICE reimbursement decisions for BTKi's in CLL have not been recommended according to IgHV status.[9,10] As such, no differences in the clinical effectiveness and cost-effectiveness of zanubrutinib is anticipated across these subgroups. Therefore, the subgroup of patients according to IgHV mutation status (mutated or unmutated) should be removed from 'Appendix B - Draft scope ID5079'. To align with the subgroups described in Table 1 of 'Appendix B - Draft scope ID5079', the Company suggests adding the following subgroup within the remit: • 'For people for whom fludarabine-based therapy is suitable' Furthermore, to better align with the reimbursement populations from previous NICE appraisals in CLL, the Company suggests amending the wording for the subgroup 'people for whom bendamustine-based therapy is unsuitable' to read 'for people for whom fludarabine-based and bendamustine-based therapy are unsuitable'.	subgroups have been updated to remove IgHV mutation status.

Section	Consultee/ Commentator	Comments [sic]	Action
		As such, the following subgroups of patients are considered appropriate for the appraisal of zanubrutinib in patients with untreated CLL: • For people for whom fludarabine-based therapy is suitable • For people for whom fludarabine-based therapy is unsuitable • For people for whom fludarabine-based and bendamustine-based therapy are unsuitable • For people with a 17p deletion or TP53 mutation References 2. Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, 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):1031–43. 6. Hillmen P, Eichhorst B, Brown J, Lamanna N, O'Brien S, Tam C, et al. First Interim Analysis of ALPINE Study: results of a Phase 3 Randomised Study of Zanubrutinib versus Ibrutinib in Patients with Relapsed/ Refractory Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma. British journal of haematology. 2022;197(SUPPL 1):92-93 7. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology. 2022;197(5):544–57.	

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		9. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation [TA429] [Internet]. 2017 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta429 10. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia [TA689] [Internet]. 2021. Available from: https://www.nice.org.uk/guidance/ta689	
	Leukaemia Care	**Relapsed or refractory CLL** Our understanding is that IGHV status is only relevant for those who are not 17p deleted or TP53 mutated.	Thank you for your comment. The subgroups have been updated to remove IgHV mutation status.
	UK CLL FORUM	**Relapsed or refractory CLL** Current subgroups under consideration in the draft guidance are • people with a 17p deletion or TP53 mutation • IgHV mutation status (mutated or unmutated) Not sure how useful it would be to pull out this second subgroup in terms of drug access. This has not been done as part of other BTKi or Venetoclax approvals in the UK. It would however be useful to add consideration of patients with intolerance or contraindication to other BTK inhibitors who have indications for retreatment **Untreated CLL** Could combine last 2 groups ie unsuitable for Fludarabine OR bendamustine ?also consider patients already taking an anticoagulant as they were included in this trial and excluded from most other trails	Thank you for your comment. The subgroups have been updated to remove IgHV mutation status

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	BeiGene UK	**Relapsed or refractory CLL** According to the anticipated place of zanubrutinib in the treatment pathway, the appropriate comparators are as follows: • Ibrutinib [NICE TA429][9] • Acalabrutinib [NICE TA689][10] A 'sequencing' approach is recommended in the 2022 BSH guidelines when selecting the optimal strategy for patients who have relapsed following treatment with front-line targeted agents.[7] The use of a 'sequencing' approach in clinical practice was confirmed by feedback received from five UK clinicians, gathered in double-blinded 1:1 interviews conducted by the Company.[8] Whilst venetoclax-rituximab is recommended by NICE for treating relapsed or refractory CLL, it is only suitable for patients who are BTKi-experienced. Hence patients eligible for zanubrutinib – namely, relapsed or refractory, BTKi-naïve patients – are not a comparable patient population. This was confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[8] The introduction of zanubrutinib will therefore not alter the decision of whether to treat with a BCL2i-based regimen or BTKi following relapse. As the initial choice of treatment class will drive the eligibility for second-line treatment, venetoclax-rituximab is not considered an appropriate comparator within the appraisal of zanubrutinib for treating relapsed or refractory CLL. Furthermore, a number of treatments listed as comparators within 'Appendix B - Draft scope ID5078' are not considered appropriate: • The following therapies are only recommended within the 2022 BSH guidelines for relapsed patients who are unsuitable for or who are refractory to a BTKi-based treatment, and hence would not be eligible for treatment with zanubrutinib.[7] Furthermore, the use of these	Thank you for your comment. The comparators have been kept broad to capture all potential options. The company may choose to exclude comparators from its submission, but should provide clear justification for doing so.

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		treatments in clinical practice is limited as confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[8] As such, these therapies should not be included in the decision problem: o Idelalisib-rituximab [NICE TA359][11] o Venetoclax monotherapy [NICE TA796][12] o Allogeneic stem cell transplantation (ASCT) ▪ It should be noted that ASCT was not considered an appropriate comparator within the NICE scope for previous appraisals of BTKis in CLL.[9,10] • The following historic therapies are no longer considered standard of care and are not recommended within the 2022 BSH guidelines.[7] Furthermore, the use of these treatments in clinical practice is limited as confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company:[8] o FCR [NICE TA193][13] o Fludarabine monotherapy [NICE TA29][14] ▪ It should be noted that fludarabine monotherapy was not considered an appropriate comparator within the NICE scope for previous appraisals of BTKis in CLL.[9,10] • The following therapies are not approved by NICE and as such, are not considered relevant to this appraisal: o Acalabrutinib-rituximab o Ibrutinib-rituximab Furthermore, it should be noted that the NICE recommendation for venetoclax monotherapy states that the treatment is only recommended for i) people with a 17p deletion or TP53 mutation when a patient's disease has progressed after a B-cell receptor pathway inhibitor and ii) people without a 17p deletion or TP53 mutation whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor. As a	

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		consequence, venetoclax monotherapy would not be considered as an alternative to zanubrutinib in relapsed or refractory patients as for patients to be eligible for venetoclax monotherapy, they would already have had to progress following treatment with a BTKi. As such, venetoclax monotherapy would not be considered a relevant comparator to zanubrutinib within this subgroup of patients. **Untreated CLL** **People without a 17p deletion or TP53 mutation** People for whom fludarabine-based therapy is suitable According to the anticipated place of zanubrutinib in the treatment pathway, the appropriate comparators are as follows: • FCR [NICE TA174][15] People for whom fludarabine-based therapy is unsuitable According to the anticipated place of zanubrutinib in the treatment pathway, the appropriate comparators are as follows: • Bendamustine-rituximab [NICE TA216][16] People for whom fludarabine-based therapy and bendamustine-based therapy are unsuitable According to the anticipated place of zanubrutinib in the treatment pathway, the appropriate comparators are as follows: • Acalabrutinib [NICE TA689][10] As highlighted in the 2022 BSH guidelines, the treatment decision in choosing the optimal front-line therapy is based on a number of factors including	Thank you for your comment. The comparators have been kept broad to capture all potential options.

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		patient- and clinician-choice.[7] As zanubrutinib is a second-generation BTKi, the introduction of zanubrutinib into the pathway will not fundamentally alter the treatment sequencing decision as to whether to initiate on a BTKi or a BCL2i-based regimen. As such, venetoclax-obinutuzumab is not considered an appropriate comparator within the appraisal of zanubrutinib for untreated CLL given that clinicians will be considering zanubrutinib as an alternative BTKi treatment to acalabrutinib if they choose to initiate with a BTKi-based regimen. In addition, feedback received from five UK clinicians, gathered in double- blinded, 1:1 interviews conducted by the Company, suggested that venetoclax-obinutuzumab was typically used to treat more 'fit' patients who are younger and do not present with comorbidities given the risk of tumour lysis and gastrointestinal (GI) side effects. As such, venetoclax-obinutuzumab is typically used within the subgroup of patients for whom fludarabine-based therapy or bendamustine-based therapy is suitable. In comparison, acalabrutinib would typically be prescribed for elderly patients or patients with comorbidities that would be unsuitable for fludarabine-based therapy and bendamustine-based therapy.[8] Furthermore, a number of treatments listed as comparators within 'Appendix B - Draft scope ID5079' are not considered appropriate for untreated people for whom fludarabine-based therapy and bendamustine-based therapy are unsuitable: • Due to the availability of more targeted front-line therapies, the following therapies are no longer considered standard of care and are not recommended within the 2022 BSH guidelines.[7] Furthermore, the use of these treatments in clinical practice is limited as confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company:[8] o Obinutuzumab-chlorambucil [NICE TA343][17]	

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		• The following therapies are not approved by NICE and as such, are not considered relevant to this appraisal: ○ Ibrutinib-venetoclax **People with a 17p deletion or TP53 mutation** According to the anticipated place of zanubrutinib in the treatment pathway, the appropriate comparators are as follows: • Acalabrutinib [NICE TA689][10] • Ibrutinib [NICE TA429][9] As highlighted in the 2022 BSH guidelines, the treatment decision in choosing the optimal front-line therapy is based on a number of factors including patient- and clinician-choice.[7] As zanubrutinib is a second-generation BTKi, the introduction of zanubrutinib into the pathway will not fundamentally alter the treatment decision as to whether to initiate on a BTKi or a BCL2i-based regimen. Furthermore, the 2022 BSH guidelines state that upfront treatment with a BTKi is preferred for patients with a 17p deletion or TP53 mutation over upfront treatment with a BCL2i-based regimen, and as such, venetoclax-obinutuzumab is not considered an appropriate comparator within the appraisal of zanubrutinib for untreated CLL given that clinicians will be considering zanubrutinib as an alternative BTKi treatment to acalabrutinib and ibrutinib if they choose to initiate with a BTKi-based regimen.[7] In addition, feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company, suggested acalabrutinib would typically be prescribed for unfit patients or for high risk patients who have 17p deletion or TP53 mutation (reflecting the zanubrutinib trial populations and anticipated place in therapy) and that usage of venetoclax-obinutuzumab was limited in this population as it is typically used to treat more 'fit' patients given the risk of tumour lysis and GI side effects.[8] Furthermore, a number of treatments listed as comparators within 'Appendix B - Draft scope ID5079' are	

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		not considered appropriate for untreated patients with a 17p deletion or TP53 mutation: • The following therapies are only recommended within the 2022 BSH guidelines for relapsed patients with a 17p deletion or TP53 mutation who are unsuitable for or who are refractory to a BTKi- or BCL2i-based treatment and not patients with untreated CLL.[7] Furthermore, the use of these treatments in clinical practice is limited as confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company:[8] o Idelalisib-rituximab [NICE TA359][11] o Venetoclax monotherapy [NICE TA796][12] • The following therapies are not considered standard of care and are not recommended within the 2022 BSH guidelines.[7] Furthermore, the use of these treatments in clinical practice is limited as confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company:[8] o FCR [NICE TA174][15] o Bendamustine monotherapy [NICE TA216][16] o Bendamustine- rituximab [NICE TA216][16] o Obinutuzumab-chlorambucil [NICE TA343][17] • The following therapies are not approved by NICE and as such, are not considered relevant to this appraisal: o Ibrutinib-venetoclax Furthermore, it should be noted that, as highlighted in the 2022 BSH guidelines, the European Medicines Agency (EMA) has amended the licence of idelalisib-rituximab to "first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies" due to the higher risk of infection and death associated with the treatment.[7] Similarly, the MHRA updated the licence with matching wording.[18]	

Section	Consultee/ Commentator	Comments [sic]	Action
		As such, idelalisib-rituximab would not be considered a relevant comparator to zanubrutinib within this subgroup of patients. References 7. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology. 2022;197(5):544–57. 8. BeiGene. Data on file. 2022; 9. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation [TA429] [Internet]. 2017 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta429 10. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia [TA689] [Internet]. 2021. Available from: https://www.nice.org.uk/guidance/ta689 11. National Institute for Health and Care Excellence. Idelalisib for treating chronic lymphocytic leukaemia [TA359] [Internet]. 2015 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta359 12. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia [TA796] [Internet]. 2022 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta796 13. National Institute for Health and Care Excellence. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia [TA193] [Internet]. 2010 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta193	

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		14. National Institute for Health and Care Excellence. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia [TA29] [Internet]. 2001 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta29 15. National Institute for Health and Care Excellence. Rituximab for the first-line treatment of chronic lymphocytic leukaemia [TA174] [Internet]. 2009 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta174 16. National Institute for Health and Care Excellence. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia [TA216] [Internet]. 2011 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta216 17. National Institute for Health and Care Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia [TA343] [Internet]. 2015 [cited 2022 Aug 25]. Available from: https://www.nice.org.uk/guidance/ta343 18. Idelalisib (Zydelig▼): updated indications and advice on minimising the risk of infection [Internet]. GOV.UK. [cited 2022 Sep 7]. Available from: https://www.gov.uk/drug-safety-update/idelalisib-zydelig-updated-indications-and-advice-on-minimising-the-risk-of-infection	
	Leukaemia Care	**Relapsed or refractory CLL** We would like clarification on the comparator: “rituximab in combination with fludarabine and cyclophosphamide, except when the condition is refractory to fludarabine or has been previously treated with rituximab”. There are several regimens listed that are comparators that involve rituximab, but this suggests that any use of rituximab outside FCR is not a comparator. We also believe that FCR is a comparator now very rarely used for CLL in the relapsed and refractory space. Therefore, the above comparator and also the use fludarabine alone is unlikely to be relevant in the context of standard NHS practice.	Thank you for your comment. The comparators have been kept broad to capture all potential options.

Section	Consultee/ Commentator	Comments [sic]	Action
		Additionally, acalabrutinib and ibrutinib with rituximab are not NICE approved comparators. Allogeneic transplantation is rare in CLL patients. It would only apply to small and heterogenous subgroup of patients. **<u>Untreated CLL</u>** The inclusion of this statement: “venetoclax, for people for whom a B cell receptor pathway inhibitor is unsuitable” is confusing. Zanubrutinib is a B cell receptor pathway inhibitor, so more clarification is need on whether monotherapy of venetoclax is or is not a comparator using the above wording. Ibrutinib with venetoclax is not yet NICE approved, so it is not typically used on the NHS. Our understanding is that bendamustine is still an option within guidelines written for CLL, for IGHV mutated patients. Chlorambucil is rarely recommended.	Thank you for your comment. The comparators have been kept broad to capture all potential options. The company may choose to exclude comparators from its submission, but should provide clear justification for doing so.
	UK CLL FORUM	**<u>Relapsed or refractory CLL</u>** A comprehensive list of comparators has been provided in the draft remit. In practice, however, in the UK in 2022, not all of these options are in regular use. Neither Acalabrutinib nor Ibrutinib can be used in combination with Rituximab under the terms of NICE/ Blueteq approval which is for monotherapy only. So these two options are not comparators within the NHS in the UK. We would consider the main comparators i.e. those in regular use to be –	Thank you for your comment. The comparators have been updated to reflect this and have been kept broad.

Section	Consultee/ Commentator	Comments [sic]	Action
		• venetoclax, for people with a 17p deletion or TP53 mutation whose disease has progressed after a B-cell receptor pathway inhibitor or people without a 17p deletion or TP53 mutation whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor • acalabrutinib, for previously treated CLL • venetoclax with rituximab, for people who have had at least 1 previous therapy • ibrutinib, for people who have had at least 1 previous therapy **<u>Untreated CLL</u>** A comprehensive list of all available comparators has been provided in the draft remit. The NICE appraisal of combination of Ibrutinib and Venetoclax is not yet complete. In practice, however, in the UK in 2022, not all of these options are in regular use. We would consider the main comparators i.e. those in regular use to be – For people without a 17p deletion or TP53 mutation, established clinical management without zanubrutinib, including (but not limited to): • acalabrutinib, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable • venetoclax and obinutuzumab, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable • obinutuzumab with chlorambucil, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable For people with a 17p deletion or TP53 mutation, established clinical management without zanubrutinib, including (but not limited to): • acalabrutinib	Thank you for your comment. The comparators have been kept broad.

Section	Consultee/ Commentator	Comments [sic]	Action
		• venetoclax and obinutuzumab • venetoclax, for people for whom a B-cell receptor pathway inhibitor is unsuitable • ibrutinib, for people for whom chemo-immunotherapy is unsuitable	
Outcomes	BeiGene UK	All outcomes listed are appropriate.	Thank you for your comment. No action needed.
	UK CLL FORUM	**Relapsed or refractory CLL** Outcomes listed are appropriate with a particular focus on adverse effects in comparison to other BTKis **Untreated CLL** Outcomes listed are appropriate with a particular focus on adverse effects in comparison to other BTKis Add time to treatment failure	Thank you for your comment. No action needed. Time to treatment failure has been added as an outcome in the scope.
Equality	BeiGene UK	There are no significant equality considerations associated with this appraisal. As CLL is largely a disease of the elderly there is a need for new treatment options that are well tolerated and suitable for those who are immunosuppressed or who have considerable comorbidities. Zanubrutinib is a simple oral regimen and does not require frequent hospital visits as with other CLL treatments which require intravenous administration. Furthermore, zanubrutinib is a BTKi with improved pharmacological properties resulting in sustained disease control and with greater selectivity. Zanubrutinib will therefore be a welcomed treatment option for older, frail or less fit patients.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK CLL FORUM	**Relapsed or refractory CLL** Delivered orally – no equality issues that I am aware of. **Untreated CLL** No equality issues that I am aware of. As an oral medication Zaubrutinib is easy to deliver across all patients groups when compared with conventional chemo-immunotherapy such as Bendamustine and Rituximab	Thank you for your comment. No action needed.
Other considerations	BeiGene UK	There are no additional issues to comment on.	Thank you for your comment. No action needed.
	Leukaemia Care	Zanubrutinib should be a candidate for managed access, especially to allow further comparison with other comparators	Thank you for your comment. No action needed.
	UK CLL FORUM	**Relapsed or refractory CLL** In the Alpine trial, preliminary evidence suggests that patients with RR CLL/SLL who received zanubrutinib monotherapy reported improvements in key HRQOL end points compared with patients who received ibrutinib monotherapy. Hillmen P, Brown J, Lamanna N, et al. Health-related quality of life outcomes associated with zanubrutinib vs ibrutinib monotherapy in patients with relapsed/refractory (RR) CLL/SLL: results from the randomized phase 3 ALPINE trial. HemaSphere. 2022;6(suppl 3):P663	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		<u>Untreated CLL</u> Consider whether zanubrutinib could be made available across all patient groups; not just those considered unsuitable for BR or FCR, as in the SEQUOIA trial. We have evidence that the benefit of Ibrutinib (used with Rituximab) extends to younger patients and actually provides on OS advantage when compared with chemo-immunotherapy. We would expect zanubrutinib to have the same benefit. This younger patient group is currently unable to access front line BTK inhibitors in the UK. This is an unmet need. D D. Shanafelt, M.D., Xin V. Wang, Ph.D.et al Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med 2019; 381:432-443 Also preliminary evidence has been presented that QOL measures are improved on zanubrutinib. Ghia P, Barnes G, Yang K, et al. Patient-reported outcomes from a phase 3 randomized study of zanubrutinib versus bendamustine plus rituximab (BR) in patients with treatment-naïve (TN) CLL/SLL. HemaSphere. 2022;6(suppl):P662	Thank you for your comment. No action needed.
Questions for consultation	BeiGene UK	As zanubrutinib is a second-generation BTKi, with comparable efficacy expected against alterative BTKi options, namely ibrutinib and acalabrutinib, a cost-comparison methodology would be deemed appropriate for this appraisal. The Company does not consider zanubrutinib a candidate for managed access or a ‘step-change’ in the management of CLL.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag	**<u>Relapsed or refractory CLL</u>** **Have all relevant comparators for zanubrutinib been included in the scope?** Yes **Are acalabrutinib with rituximab and ibrutinib with rituximab currently used in NHS clinical practice for relapsed or refractory CLL?** No, only ibrutinib monotherapy or acalabrutinib monotherapy are currently used in this setting. Imbruvica in combination with bendamustine and rituximab (BR) (Helios study) is indication for the treatment of adult patients with CLL who have received at least one prior therapy, but this is not currently reimbursed in England. **Is allogeneic stem cell transplant currently used in NHS clinical practice for relapsed or refractory CLL?** Yes. British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) indications for allogeneic transplantation in CLL remain as defined in 2013 (https:// bsbmt ct.org/). This therapy continues to be an option for patients withhigh-risk features such as *TP53* disruption and treatment failure. The decision to transplant patients should be based on remission status, patient age, performance status, comorbidity and patient preference, donor status and availability of alternative treatments. The British Society for Haematology (BSH) guidelines for the treatment of CLL recommended Allogeneic stem cell transplantation (AlloSCT) as a treatment option for suitable patients with high-risk CLL defined by either: (i) failed two out of chemoimmunotherapy, BCRi and/or BCL2i irrespective of *TP53* status, or (ii) failed either BCRi and/or BCL2i therapy and harbour a *TP53* disruption.	Thank you for your comment. No action needed. Thank you for your comment. The comparators have been updated. Thank you for your comment. Allogeneic stem cell transplant has not been included as a comparator.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the outcomes listed appropriate? Yes **Are people with a 17p deletion or TP53 mutation according to IgHV mutation status (mutated or unmutated) appropriate subgroups?** The BCSH guidelines (Walewska et al., BJHaem 2022) state that the current licensed therapies in relapsed CLL are BTKi (ibrutinib and acalabrutinib), BCL2i (venetoclax monotherapy or in combination with rituximab) and phosphoinositide 3-kinase inhibitors (PI3Ki) (idelalisib and rituximab). There is no data to support these patients, who participated in the Alpine study, should be treated differently in clinical practice compared to other patients with RR CLL. **Are there any other subgroups of people in whom zanubrutinib is expected to be more clinically and cost effective or other groups that should be examined separately?** No **Where do you consider zanubrutinib will fit into the existing treatment pathway for relapsed or refractory chronic lymphocytic leukaemia?** Ibrutinib monotherapy and acalabrutinib monotherapy are already licensed and NICE approved options for adult patients with previously treated CLL. Any additional BTKi could give an alternative option for patients in this setting **<u>Untreated CLL</u>**	Thank you for your comment. No action needed. Thank you for your comment. The subgroups have been updated. A 17p deletion or TP53 mutation has remained as a possible subgroup of interest. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for zanubrutinib been included in the scope? Yes. **Are bendamustine or chlorambucil-based chemo-immunotherapy regimens currently used in NHS clinical practice for previously untreated CLL?** Bendamustine or chlorambucil-based chemo-immunotherapy (CIT) are no longer recommended by British Society of Haematology (BSH) https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.18075 **Are the outcomes listed appropriate?** Yes. **Are the subgroups suggested appropriate? Are there any other subgroups of people in whom zanubrutinib is expected to be more clinically and cost effective or other groups that should be examined separately?** In the Sequoia study (zanubrutinib vs BR), the progression free survival (PFS) benefit for zanubrutinib over BR was observed across subgroups for: age, Binet stage, bulky disease, and del(11q) status. Treatment benefit was	Thank you for your comment. No action needed. Thank you for your comment. Bendamustine-rituximab is a comparator in the scope for people with untreated CLL without a 17p deletion or TP53 mutation and in whom fludarabine-based therapy is unsuitabl Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		also observed for zanubrutinib patients with unmutated IGHV, but not for mutated IGHV. Estimated 24-month overall survival (OS) demonstrated no difference between zanubrutinib vs BR cohorts. In the forest plot of the Sequoia study, the patient subgroups are in favour of zanubrutinib except patients with IgHV mutational status and TP53 mutation. There are uncertainties in these two patient groups, suggesting they are not appropriate to be included Reference: Ghia P, Barnes G, Yang K, et al. Patient-reported outcomes from a phase 3 randomized study of zanubrutinib vs bendamustine plus rituximab (BR) in patients with treatment-naive (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Presented at: 2022 EHA Congress; June 9-17, 2022; Vienna, Austria. Abstract P662. Tam CS.et al., Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol 2022 Aug;23(8):1031-1043. **Where do you consider zanubritinib will fit into the existing treatment pathway for untreated chronic lymphocytic leukaemia?** The most clinically plausible and appropriate population would be in older patients or patients with comorbidities who have untreated CLL, e.g., ≥65-year-old or unfit for FCR. The study was designed for patients who had untreated CLL or SLL requiring treatment as per International Workshop on CLL criteria; were aged 65 years or older, or 18 years or older and had comorbidities (Tam et al., Lancet Oncol	Thank you for your comment. The subgroups have been updated to remove IgHV mutation status. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		2022). This patient group is normally not suitable for chemoimmunotherapy such as FCR and BR. **<u>Both relapsed or refractory and untreated CLL</u>** **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Ibrutinib, acalabrutinib and zanubrutinib are all based on irreversible (covalent) BTK binding mechanism. So, it is likely to be similar in clinical efficacy and resource use to any of the comparators. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** PFS is a more clinically relevant and important treatment outcome than ORR. In the Alpine study (zanubrutinib vs ibrutinib) for RR CLL, the primary endpoint was the ORR (PR+CR) non-inferiority and superiority, as assessed by the investigator. The early ORR advantage (with a short median follow-up of 15.3 months) may not translate into statistically significant differences in the PFS in the long-term; the statistical assumption of the ORR differences is not known. Investigator-assessment is less rigorous compared to IRC-assessment. In the Sequoia study (zanubrutinib vs BR) for untreated CLL, the primary endpoint was PFS per IRC assessment [per modified International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria for CLL], which is clinically relevant. However, the median follow-up was 26.2 months, and so a longer follow-up is needed to demonstrate the long-term efficacy and safety profile for the trial and real-world evaluation.	Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK CLL FORUM	**<u>Relapsed or refractory CLL</u>** **Questions from the draft scope not answered above:** • Is allogeneic stem cell transplant currently used in NHS clinical practice for relapsed or refractory CLL? Allogeneic transplant may still be considered in younger fit patients who are close to exhausting current treatment options. In practice it I s carried out less frequently now as targeted agents overcome to an extent the poor prognosis associated with p53 abnormailities • Where do you consider zanubrutinib will fit into the existing treatment pathway for relapsed or refractory chronic lymphocytic leukaemia? Will be indicated for a similar patient group who currently receive Acalabrutinib, but with some evidence of usage in anticoagulated patients and potentially a better safety profile. • Would zanubrutinib be a candidate for managed access? Yes, could collect real world data. Would also be very useful to allow access for patients treated with another TKI previously and collect efficacy data. • Do you consider zanubrutinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes In interim analysis of the randomized, phase 3 ALPINE study in patients with R/R CLL/SLL, zanubrutinib was shown to have a superiority in the primary end point of investigator-assessed overall response rate, an improved PFS and a lower rate of atrial fibrillation/flutter as compared with ibrutinib. In addition, in patients with aggressive disease, at 18 months, 20 patients had disease progression on zanubrutinib compared with 42 patients on Ibrutinib, suggesting that it may have greater efficacy in high risk disease. These data confirm that more selective BTK inhibition, with more complete and sustained BTK occupancy results in improved efficacy and safety outcomes. • Do you consider that the use of zanubrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The benefits of the reduced incidence of cardiac toxicity are likely to be cumulative in the longer term and more difficult to capture in a time-limited study **<u>Untreated CLL</u>**	Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Questions from the draft scope not answered above: • Where do you consider zanubritinib will fit into the existing treatment pathway for untreated chronic lymphocytic leukaemia? As an upfront treatment for a similar patient group who currently receive Acalabrutinib, but with some evidence of safety in anticoagulated patients and potentially a better safety profile. • Would zanubrutinib be a candidate for managed access? Yes – could collect real world data, especially if access granted to younger, fitter patients • Do you consider zanubritinib 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)? Yes In the phase 3 SEQUOIA trial, zanubrutinib significantly improved progression-free survival versus bendamustine–rituximab, with an acceptable safety profile consistent with previous studies. These data support zanubrutinib as a potential new treatment option for untreated CLL.	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		There was no direct comparison with existing BTKs and it would be good to extend access to younger patients who currently have an unmet need for upfront TKI. • Do you consider that the use of zanubrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The benefits of the reduced incidence of cardiac toxicity are likely to be cumulative in the longer term and more difficult to capture in a time-limited study	Thank you for your comment. No action needed.
Any additional comments on the draft scopes	UK CLL FORUM	**Relapsed or refractory CLL** References: Results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA 2021 Virtual Congress. Abstract LB1900. Presented June 11, 2021. **Untreated CLL** **References:** Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a	Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		randomised, controlled, phase 3 trial. The Lancet Oncology, 2022 Vol: 23, Issue: 8, Page: 1031-1043	

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

CLL support