Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from BeiGene
2. **Company summary of information for patients (SIP)** from BeiGene
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Chronic Lymphocytic Leukaemia Support
   b. Leukaemia Care
   c. Lymphoma Action
   d. UK CLL Forum-British Society for Haematology
5. **External Assessment Report** prepared by Newcastle NIHR TAR
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Post-technical engagement documents

7. **Technical engagement response from company**
8. **Technical engagement responses and statements from experts:**
   a. Dr Rosalynd Johnston – clinical expert, nominated by UK CLL Forum-Royal College of Pathologists-British Society for Haematology
   b. Professor Francesco Forconi – clinical expert, nominated by BeiGene
9. **Technical engagement responses from stakeholders:**
   a. Chronic Lymphocytic Leukaemia Support
   b. Leukaemia Care
   c. UK CLL Forum- UK CLL Forum- British Society for Haematology-Royal College of Pathologists
   d. Janssen

10. External Assessment Report critique of company response to technical engagement prepared by Newcastle NIHR TAR

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID5078_Zanubrutinib for treating chronic lymphocytic leukemia Document B	V1.0	Yes	16th January 2023

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The objective of this single technology appraisal is to evaluate the clinical- and cost-effectiveness of zanubrutinib as a monotherapy for adult patients with previously untreated and relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) within its marketing authorisation. On 13 October 2022, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a change to the terms of the marketing authorisation for zanubrutinib to include the new indication for the treatment of CLL:

- BRUKINSA as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL)[1]

On 17 November 2022, marketing authorisation was subsequently granted by the European Medicines Association (EMA), followed by approval by the Medicines and Healthcare products Regulatory Agency (MHRA) through the European Commission Decision Reliance Procedure on 6 January 2023.[2,3]

The submission focuses on part of the technology's marketing authorisation. An assessment in the subpopulation of previously untreated patients suitable for fludarabine, cyclophosphamide and rituximab-based therapy (FCR) or bendamustine and rituximab-based therapy (BR) is omitted given the lack of clinical trial evidence available for zanubrutinib in this population. Whilst a cost-effectiveness assessment in this population has not been provided, it is plausible to assume that zanubrutinib might be cost-effective in this population (see B.1.4 Equality considerations for further details).

The Company is seeking reimbursement in the following patient populations to align with the availability of data and the expected use of zanubrutinib in clinical practice in the United Kingdom (UK):

A. Previously untreated adults with CLL who are unsuitable for FCR and BR therapy

B. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy (CIT) is unsuitable

C. Adults with R/R CLL who have had at least one previous therapy

The submission presents data for the following outcomes: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), time-to-treatment failure (TTTF), adverse events (AEs), and health-related quality of life (HRQoL), which is consistent with the decision problem outlined by the National Institute for Health and Care Excellence (NICE) in the final scope. The economic analysis follows the NICE reference case and therefore ensures alignment with the NICE decision problem for zanubrutinib.

B.1.1.1 Comparators

Several treatments are listed within the final scope, however only a small number of these are considered relevant comparators to zanubrutinib in the patient populations relevant to this appraisal.

A. Previously untreated adults with CLL who are unsuitable for FCR and BR therapy

According to the anticipated place of zanubrutinib in the treatment pathway, the most appropriate comparator for previously untreated adults with CLL who are unsuitable for FCR and BR therapy is **acalabrutinib**.[4]

As per the 2022 British Society for Haematology (BSH) guidelines, the treatment choice in the first-line setting is between a Bruton tyrosine kinase inhibitor (BTKi), namely acalabrutinib or ibrutinib, or a venetoclax-based regimen with the decision influenced by a number of factors including patient- and clinician-choice.[5] In this population, only acalabrutinib is recommended by NICE of the two BTKis and venetoclax-obinutuzumab reflects the only recommended venetoclax-based regimen.[4,6]

UK prescribing data for a sample of [redacted] patients with CLL collected by IQVIA in December 2022, reported that in untreated patients who are considered unfit (defined as patients aged >65 or patient age ≤65 with comorbidities), [redacted]% are treated with BTKis. In contrast, only [redacted]% of unfit patients receive treatment with a venetoclax-based regimen.[7] These findings were supported by an online quantitative survey of 30 UK-based CLL specialists conducted by the Company and by feedback from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[8,9] Within the interviews, clinicians confirmed 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 syndrome and gastrointestinal (GI) side effects.[8,9] As such, venetoclax-obinutuzumab is typically used within the subgroup of patients for whom FCR or BR therapy

is suitable. In contrast, acalabrutinib would typically be prescribed for elderly patients or patients with comorbidities that would be unsuitable for FCR and BR therapy.[10]

Furthermore, feedback gathered from five UK experts (two clinical experts; two health economic experts; one statistical expert) at an advisory board (03 November 2022) conducted by the Company supported the positioning of zanubrutinib as an alternative BTKi treatment option and not as alternative to venetoclax-obinutuzumab. The experts confirmed that the introduction of zanubrutinib would not change the decision of whether to treat with a venetoclax-based regimen or a BTKi and as such, alternative BTKis would be considered the key comparators of interest.[11]

As zanubrutinib is a next-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 B-cell lymphoma 2 inhibitor (BCL2i, i.e. a venetoclax-based regimen). As such, venetoclax-obinutuzumab is not deemed an appropriate comparator within the appraisal of zanubrutinib for patients with previously untreated CLL given that clinicians will consider zanubrutinib to be an alternative BTKi option to acalabrutinib if they choose to initiate with a BTKi-based regimen.

Prior to the approval of targeted agents, chlorambucil-obinutuzumab was established as standard of care in this cohort. As per the 2022 BSH CLL guidelines, chlorambucil-based CIT is no longer recommended since targeted pathway inhibitors have represented a paradigm shift in front-line treatment.[5] UK prescribing data for patients with CLL collected by IQVIA in December 2022, supports the declining use of chlorambucil-based CIT with only [redacted]% of unfit patients receiving this therapy.[7] Furthermore, the limited use of chlorambucil-based CIT in clinical practice was confirmed in a quantitative survey conducted by the Company and by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company, and from UK clinical experts in attendance at an advisory board (03 November 2022) conducted by the Company.[8,9,11] Chlorambucil-obinutuzumab, chlorambucil-rituximab and chlorambucil monotherapy are therefore not considered relevant comparators in this population.[12]

FCR and BR are not considered standard of care in this cohort by definition as patients are deemed unsuitable for CIT and are not recommended within the 2022 BSH guidelines in this population of patients.[13,14] Furthermore, the use of these treatments in clinical practice is declining as confirmed by UK prescribing data for patients with CLL collected by IQVIA in December 2022 ([redacted]%) and a quantitative survey conducted by the Company.[7,8] Feedback

received from five UK clinicians, gathered in double-blinded 1:1 interviews and an advisory board (03 November 2022) conducted by the Company further supported this conculsion.[10,11] These therapies are therefore not considered relevant comparators to zanubrutinib in this appraisal.

Ibrutinib-venetoclax is subject to an ongoing NICE appraisal (ID3860) and is neither routinely commissioned by NHS England, nor does it reflect established NHS clinical practice.[15] As such, it is not considered a relevant comparator to zanubrutinib in this appraisal.

B. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable

According to the anticipated place of zanubrutinib in the treatment pathway, the most appropriate comparators for previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable are **acalabrutinib** and **ibrutinib**.[4,16]

As per the 2022 BSH guidelines, the treatment choice in the first-line setting is between acalabrutinib, ibrutinib and venetoclax-obinutuzumab and is influenced by a number of factors including patient- and clinician-choice.[5,6] Whilst venetoclax-obinutuzumab is considered as an option in this population, the 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 (i.e. a venetoclax-based regimen).[5]

Feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company, suggested BTKis would typically be prescribed for previously untreated patients with a 17p deletion or TP53 mutation 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 syndrome and GI side effects.[9] This was supported by UK prescribing data for patients with CLL collected by IQVIA in December 2022, in which [redacted]% of untreated patients with a 17p deletion or TP53 mutation were treated with a BTKi, and by a quantitative survey conducted by the Company.[7,8] Furthermore, feedback gathered from a UK advisory board (03 November 2022) conducted by the Company supported the positioning of zanubrutinib as an alternative BTKi treatment option in this patient population, with experts noting that 'high-risk' patients would typically receive treatment with a BTKi.[11]

As zanubrutinib is a next-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. As such, venetoclax-obinutuzumab is not deemed an appropriate

comparator within the appraisal of zanubrutinib for patients with previously untreated CLL who have a 17p deletion or TP53 mutation given that clinicians will be considering zanubrutinib to be an alternative BTKi option to acalabrutinib and ibrutinib if they choose to initiate with a BTKi-based regimen.

Idelalisib-rituximab and venetoclax monotherapy are not considered standard of care in this cohort and are only recommended within the 2022 BSH guidelines in treating 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.[5] As such, these treatments are recommended as treatment options in the absence of BTKi- or BCL2i-based treatment and not instead of. Furthermore, the use of these treatments in clinical practice is limited as confirmed by UK prescribing data for patients with CLL collected by IQVIA in December 2022 ([redacted]) and by a quantitative survey conducted by the Company.[7,8] In addition, feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company further supported this conclusion.[9] These therapies are therefore not considered relevant comparators to zanubrutinib in this appraisal.[17,18]

C. Adults with R/R CLL who have had at least one previous therapy

According to the anticipated place of zanubrutinib in the treatment pathway, the appropriate comparators for zanubrutinib in adults with R/R CLL who have had at least one previous therapy are **ibrutinib** and **acalabrutinib**.[4,16]

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.[5] The ‘sequencing’ approach suggests that the optimal treatment following progression varies depending on the front-line therapy – for patients progressing following front-line treatment with a BTKi (i.e. ibrutinib or acalabrutinib), a BCL2i regimen (i.e. venetoclax-based regimen) is recommended and for patients progressing following front-line treatment with a BCL2i, a BTKi regimen is recommended. 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.[9] Furthermore, feedback gathered from UK experts at an advisory board (03 November 2022) conducted by the Company supported the positioning of zanubrutinib as an alternative BTKi treatment

option in this patient population, with experts agreeing with the treatment sequencing concept.[11]

Whilst venetoclax-rituximab is recommended by NICE for treating R/R CLL, it is primarily used in patients previously treated with a BTKi.[19] Patients eligible for zanubrutinib are those who have not previously received treatment with a BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial[20]), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib. This was confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[9] Furthermore, feedback gathered from UK experts at an advisory board (03 November 2022) conducted by the Company supported the sequencing concept in that patients previously treated with a BTKi would receive treatment with venetoclax-rituximab in the R/R setting.[11] Whilst venetoclax-rituximab may be used in patients who have not previously received treatment with a BTKi (i.e. in patients who have previously received a venetoclax-based regimen in the front-lint setting), it was noted that this would only represent a small subset of patients who are unable or unwilling to receive treatment with a BTKi or may respond well to being rechallenged with venetoclax. However, as noted in the 2022 BSH guidelines there is a distinct lack of data on rechallenging patients with a venetoclax-based regimen.[5]

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 R/R CLL.

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 CIT and a B-cell receptor pathway inhibitor.[18] As a consequence, venetoclax monotherapy would not be considered as an alternative to zanubrutinib in patients with R/R CLL 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.

Similarly, idelalisib-rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment. As such, idelalisib-rituximab would be considered a third-line (or beyond) therapy.[17]

A summary of the comparators considered relevant for this appraisal is presented in Table 1.

Table 1. Comparators considered relevant for this appraisal

Comparator listed in the final scope	Relevance to this appraisal	Rationale
Previously untreated adults with CLL who are unsuitable for FCR and BR therapy		
Acalabrutinib	✓	**Key comparator**
Venetoclax with obinutuzumab	×	An alternative treatment option to BTKis, low usage in the 'unfit' population and typically used to treat more 'fit' patients as supported by UK prescribing data and UK clinical expert feedback [7,11]
Chlorambucil with or without rituximab	×	No longer recommended as per 2022 BSH CLL guidelines[5] and low usage confirmed by UK prescribing data
Obinutuzumab with chlorambucil	×	
BR	×	Patients are ineligible for BR in this population by definition
FCR	×	Patients are ineligible for FCR in this population by definition
Ibrutinib with venetoclax	×	Not approved by NICE
Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable		
Acalabrutinib	✓	**Key comparator**
Ibrutinib	✓	**Key comparator**
Venetoclax with obinutuzumab	×	Low usage in population; typically used in fitter patients; usage unlikely to change with introduction of zanubrutinib, as supported by UK prescribing data and UK clinical expert feedback [7,11]
Venetoclax monotherapy	×	Not recommended in patients who have not previously received treatment with a BTKi patients, which is the population eligible for zanubrutinib
Idelalisib with rituximab	×	
Adults with R/R CLL who have had at least one previous therapy		
Acalabrutinib	✓	**Key comparator**
Ibrutinib	✓	**Key comparator**
Venetoclax with rituximab	×	Not recommended in patients who have not previously received treatment with a BTKi, which is the population eligible for zanubrutinib
Venetoclax	×	
Idelalisib with rituximab	×	

BR – Bendamustine-rituximab; BSH – British Society for Haematology; BTKi – Bruton's tyrosine kinase inhibitor; CDF – Cancer Drugs Fund; CIT – chemo-immunotherapy; CLL – chronic lymphocytic leukaemia; FCR – Fludarabine, cyclophosphamide and rituximab; NICE – National Institute for Health and Care Excellence; R/R – relapsed/refractory.

Table 2 presents an overview of the decision problem addressed by the Company submission and the rationale for any deviation from the final NICE scope.

Table 2: The decision problem

Aspect	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
Population	People with chronic lymphocytic leukaemia	As per scope	N/A
Intervention	Zanubrutinib	As per scope	N/A
Comparator(s)	For untreated CLL, including (but not limited to): • acalabrutinib (17p deletion or TP53 mutation or if fludarabine or bendamustine-based regimens are not suitable) • ibrutinib (17p deletion or TP53 mutation) • ibrutinib with venetoclax (subject to ongoing NICE appraisal) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab • fludarabine, cyclophosphamide and rituximab • venetoclax with obinutuzumab	Previously untreated adults with CLL who are unsuitable for FCR and BR therapy: • acalabrutinib Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable: • acalabrutinib • ibrutinib Adults with R/R CLL who have had at least one previous therapy: • acalabrutinib • ibrutinib	Previously untreated adults with CLL who are unsuitable for FCR and BR therapy: • FCR, BR: Not considered standard of care in this cohort by definition as patients are deemed unsuitable for therapy. Low usage confirmed by UK prescribing data with [redacted]% of unfit (defined as patients aged >65 years or patient age ≤65 with comorbidities) patients receiving these therapies.[7] • Venetoclax-obinutuzumab: Low usage of venetoclax-obinutuzumab in this population as confirmed by UK prescribing data which reported that [redacted]% of unfit, previously untreated patients are treated with BTKis. In contrast, only [redacted]% of unfit patients receive treatment with a venetoclax-based regimen.[7] Feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews and an advisory board (03 November 2022) conducted by the Company, supported that venetoclax-obinutuzumab usage in this population was low and it was typically used to treat more 'fit' patients who are younger and do not present with comorbidities given the risk of tumour lysis syndrome and GI side effects. These patients would typically be eligible for FCR and/or BR and as such, the treatment is not relevant to this population.

Aspect	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
	• venetoclax (17p deletion or TP53 mutation and if B-cell receptor pathway inhibitor is unsuitable) For relapsed or refractory CLL, including (but not limited to): • acalabrutinib • ibrutinib • venetoclax (if disease has progressed after a B-cell receptor pathway inhibitor) • venetoclax with rituximab • idelalisib with rituximab		• Chlorambucil with or without rituximab or obinutuzumab: Chlorambucil-based CIT is no longer recommended since targeted pathway inhibitors have represented a paradigm shift in front-line treatment.[5] Low usage of chlorambucil-based CIT in this population as confirmed by UK prescribing data with only [redacted]% of unfit patients receiving this therapy.[7] • Ibrutinib-venetoclax: Subject to an ongoing NICE appraisal (ID3860) and is neither routinely commissioned by NHS England, nor does it reflect established NHS clinical practice. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable: • Venetoclax-obinutuzumab: 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. Low usage of venetoclax-obinutuzumab in this population as confirmed by UK prescribing data, with [redacted]% of untreated patients with a 17p deletion or TP53 mutation being treated with a BTKi and [redacted]% receiving treatment with venetoclax-obiutuzumab.[7] Furthermore, feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews and an advisory board (03 November 2022) conducted by the Company, supported that venetoclax-obinutuzumab usage in this population was low and it was typically used to treat more 'fit' patients who are younger and do not present with comorbidities given the risk of tumour lysis syndrome and GI side effects. These patients would typically be eligible for FCR and/or BR and as such, the treatment is not relevant to this population.

Aspect	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
			• Idelalisib-rituximab, venetoclax monotherapy: Only recommended for relapsed patients who are unsuitable for or who are refractory to a BTKi-based treatment, i.e. in patients not eligible for treatment with zanubrutinib with low usage in this population as supported by UK prescribing data ([redacted]). Adults with R/R CLL who have had at least one previous therapy: • Venetoclax-rituximab: Treatment 'sequencing' suggests that the optimal treatment following progression varies depending on the front-line therapy – 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. Whilst venetoclax-rituximab is recommended by NICE for treating R/R CLL, it is primarily used in patients previously treated with a BTKi.[19] Patients eligible for zanubrutinib are those who have not previously received treatment with a BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial[20]), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib. • Venetoclax monotherapy: 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 CIT and a B-cell receptor pathway inhibitor, i.e. in patients not eligible for

Aspect	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
			treatment with zanubrutinib. • Idelalisib-rituximab: Only recommended for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment, i.e. in patients not eligible for treatment with zanubrutinib.
Outcomes	• overall survival • progression-free survival • response rate • time-to-treatment failure • adverse effects of treatment • health-related quality of life	As per scope	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The	Cost-effectiveness of zanubrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR therapy: • Cost-minimisation analysis of zanubrutinib vs. acalabrutinib. Cost-effectiveness of zanubrutinib in previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable: • Cost-minimisation analysis of zanubrutinib vs. acalabrutinib and ibrutinib. Cost-effectiveness of zanubrutinib in adults with R/R	N/A

Aspect	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
	availability and cost of biosimilar and generic products should be taken into account.	CLL who have had at least one previous therapy: • Cost-minimisation analysis of zanubrutinib vs. acalabrutinib and ibrutinib.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Untreated CLL • Relapsed or refractory CLL Within untreated CLL, if the evidence allows the following subgroups may be considered: • People for whom fludarabine-based therapy is suitable • People for whom fludarabine-based therapy is unsuitable • People for whom fludarabine-based and bendamustine-based therapy are unsuitable • People with a 17p deletion or TP53 mutation	The following subgroups will be considered: • Untreated CLL • Relapsed or refractory CLL Within untreated CLL, the following subgroups of patients are considered appropriate: • People for whom fludarabine-based and bendamustine-based therapy are unsuitable • People with a 17p deletion or TP53 mutation	Assessments in the following subpopulations of patients with untreated CLL are omitted given the lack of clinical trial evidence available for zanubrutinib in this population: • People for whom fludarabine-based therapy and/or bendamustine-based therapy is suitable

BR – Bendamustine-rituximab; BSH – British Society for Haematology; BTKi – Bruton's tyrosine kinase inhibitor; CDF – Cancer Drug Fund; CIT – Chemo-immunotherapy; CLL – Chronic lymphocytic leukaemia; FCR – Fludarabine, cyclophosphamide and rituximab; NICE – National Institute for Health and Care Excellence; NHS – National Health Service; R/R – Relapsed/refractory

B.1.2 Description of the technology being evaluated

A description of zanubrutinib is presented in Table 3.

Table 3: Technology being evaluated

UK approved name and brand name	**UK approved name: Zanubrutinib** **Brand name: BRUKINSA®**
Mechanism of action	Zanubrutinib is a highly selective, small molecule, orally administered, irreversible inhibitor of BTK. BTK is a signalling molecule of the BCR and cytokine receptor pathways. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Zanubrutinib binds with and inhibits BTK which blocks BCR-induced BTK activation. By blocking the signalling pathway, this inhibits the proliferation and survival of malignant B cells.[21] In non-clinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.[2] Zanubrutinib is specific and selective for BTK and was designed to minimise off-target inhibition of other kinases. As such, it has the potential to improve outcomes and reduce side effects compared with first-generation BTKi's.[22]
Marketing authorisation/CE mark status	On 13 October 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for zanubrutinib, to include the new indication for the treatment of CLL: • BRUKINSA as monotherapy is indicated for the treatment of adult patients with CLL.[1] On 17 November 2022, marketing authorisation was subsequently granted by the EMA, followed by approval by the MHRA through the European Commission Decision Reliance Procedure on 6 January 2023.[2,3]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	BRUKINSA as a monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia.
Method of administration and dosage	• The recommended total daily dose of zanubrutinib is 320 mg taken orally either once daily (four x 80 mg capsules) or divided into two doses of 160 mg twice daily (two x 80 mg capsules).

	• Patients should be instructed to swallow the capsules whole with water (with or without food), and not to open, break or chew the capsules.
Additional tests or investigations	No
List price and average cost of a course of treatment	• Zanubrutinib is available at a list price of £4,928.65 for a pack of 120 x 80 mg capsules.[23]
Patient access scheme (if applicable)	• [redacted]

Source: Zanubrutinib SmPC.[2]
BCR – B-cell antigen receptor; BTK – Bruton's tyrosine kinase; CHMP – Committee for Medicinal Products for Human Use; CLL – Chronic lymphocytic leukaemia; EMA – European Medicines Agency; MHRA – Medicines and Healthcare products Regulatory Agency; PAS – Patient access scheme; SmPC – Summary of Product Characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

CLL is the most common type of leukaemia and is characterised by the abnormal clonal proliferation and accumulation of mature and typically CD5-positive B-lymphocytes within the blood, lymph nodes and spleen.[24] CLL presents more commonly in men than in women and most patients with CLL will not initially present with symptoms at diagnosis.[25] Typical cancer related symptoms associated with CLL include night sweats, fever, chills and weight loss. Clinical signs of CLL include, but are not limited to, an enlarged lymph nodes, liver, spleen and bruising. Blood counts are the most common abnormality in CLL with an increase in monoclonal lymphocytes and over time, decreased haemoglobin and platelets.[26]

B.1.3.1.1 Clinical presentation, staging and diagnosis

In the UK, a diagnosis of CLL requires the presence of ≥ 5 × 10^9/L monoclonal B-lymphocytes (5000μL) in the peripheral blood for at least 3 months as defined by the International Workshop on CLL (iwCLL).[27,28] Patients diagnosed with early-stage CLL are often asymptomatic and many of these patients will have indolent CLL for years prior to the onset of symptoms.[29,30] Once a patient is diagnosed, physical examination and complete blood counts are used to determine the clinical staging of their CLL.

The three-stage Binet staging system is predominantly used to measure the progression of CLL (primarily used in the UK and Europe) and is determined by the number of red blood cells and platelets and the number of areas in the lymphatic system that are enlarged.[27,29–31] The Binet staging system was used in the zanubrutinib clinical trials, ALPINE and SEQUOIA, and is summarised in Table 4.[20,32]

Table 4: Summary of Binet CLL staging systems

Stage	Description	Predicted median survival[a]
Binet A	Haemoglobin ≥ 10.0 g/dL, thrombocytes ≥ 100 × 10^9/L, < 3 lymph nodes involved	>10 years
Binet B	Haemoglobin ≥ 10.0 g/dL, thrombocytes ≥ 100 × 10^9/L, ≥ 3 lymph nodes involved	>8 years
Binet C	Haemoglobin < 10.0 g/dL, thrombocytes < 100 × 10^9/L	6.5 years

[a]Survival data are from Pflug et al. 2014,[33] as described by Eichorst et al. 2015[34]
CLL – chronic lymphocytic leukaemia.

The course of CLL is highly heterogeneous and is driven by an increasing number of patient and cytogenetic factors, which can be used to predict an aggressive disease course and poor prognosis. Furthermore, some of these features, such as TP53 disruption (defined by either deletion of chromosome 17p or mutation of the TP53 gene), have been shown to impact treatment responses.[35] Patients with 17p deletion or TP53 mutation are therefore defined as 'high-risk', and are often considered not suitable for CIT.[36]

Whilst clinical staging does not accurately identify patients with indolent disease, nor predict response to treatment, it has clear prognostic implications for survival. Patients classed as high-risk or with advanced-stage disease (i.e., Binet stage C) often have a poor median survival of around six years. In comparison, patients classed as low-risk or with early-stage disease (i.e., Binet stage A) have a median survival time in excess of 10 years.[33,34] Treatment is not usually recommended for asymptomatic patients with early-stage CLL and instead, it is much more common for patients to be monitored for signs of increased disease activity until symptom onset.[37] Once symptoms are observed, treatment is then initiated.[37]

Comorbidities, polypharmacy and impaired organ function can also impact the ability of patients to tolerate treatment, as can age, with elderly patients (≥65 years old) particularly affected. These 'less fit' patients are typically ineligible for intensive CIT, such as FCR.

B.1.3.1.2 Epidemiology

CLL is the most common form of leukaemia and accounts for 1% of total cancer cases in the UK (2016-18).[38] CLL is rare in people under 40 years of age and mostly affects people over 60.[39] As described in Table 5, approximately 3,803 new cases of CLL are diagnosed each year in England and Wales, equating to 10 new cases a day, with new cases more likely to develop in men than women. With an incidence 5.8 per 100,000 population (6.7 per 100,000 if age-standardised), CLL is often classified as an orphan disease. The mortality rate is high with approximately 976 CLL deaths in the UK each year, equating to nearly three deaths each day.[40] However, the recent (post-2015) introduction of more efficacious targeted therapies, will likely lead to a reduction in the mortality rate in the longer term.

Table 5: CLL incidence rates in England and Wales (2016-2018)

Data for leukaemia code C91.1.	England	Wales	UK
Number of new cases	3,331	153	3,803
European age-standardised incidence rates			
Persons	6.5 per 100,000	4.8 per 100,000	6.2 per 100,000
Men	8.8 per 100,000	6.4 per 100,000	8.5 per 100,000
Women	4.4 per 100,000	3.4 per 100,000	4.2 per 100,000

Source: Cancer research[40]
CLL – chronic lymphocytic leukaemia

B.1.3.2 Burden of CLL

CLL is a chronic disease associated with high disease morbidity and detriments to quality of life. Therefore, improving or maintaining quality of life, especially in patients with more advanced or progressed CLL is vital.[41]

B.1.3.2.1 Symptom burden

Patients with CLL can present with asymptomatic, indolent disease that may never require therapy (approximately one third of patients) or active disease that can lead to progressive lymphocytosis, cytopenias (anaemia and thrombocytopenia), lymphadenopathy, hepatosplenomegaly, B symptoms, fatigue, recurrent infections, or autoimmune complications.[28,34,42]

Patients living with symptomatic CLL experience a range of debilitating symptoms including persistent tiredness, anaemia, high temperatures, night sweats, unintentional weight loss and swollen glands.[39] In addition to this physical burden, the mental state of patients is

affected. Patients report feeling anxious and depressed with difficulties sleeping. Due to the high risk of infection, patients find that they feel isolated because of reduced social interaction.[4] In addition, after the shock of diagnosis, patients can spend a long time in the 'Watch and Wait' stage, causing anxiety and uncertainty around their prognosis.[6] In previous NICE appraisals, UK patient representatives have described having to deal with a range of debilitating symptoms that have an additional impact on their mental state (depression, stress, anxiety, worrying, difficulty sleeping).[4]

As CLL is a disease of the elderly, the majority of newly diagnosed patients have at least one comorbidity. The comorbidities are diverse and can include other malignancies, metabolic disorders, cardiovascular, and respiratory diseases, meaning that patients with CLL are taking a median of two prescription medications per day at the time of diagnosis.[43] Elderly CLL patients also tend to be 'unfit', and have impaired organ function, which together with comorbidities, impacts their ability to tolerate aggressive CIT.[55] As such, the physical fitness of patients with CLL, existing comorbidities and comedications exacerbate the burden of CLL and impacts treatment choice for patients. In total, it is estimated that [redacted]% of patients are unsuitable for treatment with FCR and BR, based on UK prescribing data for patients with CLL collected by IQVIA in December 2022.[7]

B.1.3.2.2 Impact on quality of life

As CLL is a chronic and incurable disease, patients face a huge emotional and mental burden, which can lead to depression (22.6%), anxiety (40.3%) and difficulties sleeping (34.7%).[19] In the UK, there are approximately 13,000 people with CLL who are on a 'Watch and Wait' strategy, which involves monitoring patients with CLL to track disease progression and only initiating treatment at symptom onset. The uncertainty during this period has a detrimental impact on HRQoL; over half of these patients (53%) have reported feelings of concern or anxiety since diagnosis and 12.5% of patients feeling constantly depressed and anxious.[44] However, there is limited literature available that formally quantifies the HRQoL impact of CLL on patients.[44]

The choice of treatment can also have a large impact on HRQoL in CLL. Whilst CIT was previously considered standard of care, it is associated with high rates of AEs and hence significant HRQoL issues. Targeted treatments, such as BTKis, have offered improved survival and safety profiles compared with CIT, resulting in substantial increases in

HRQoL.[45] However, first-generation BTKis remain imperfect and are associated with tolerability issues for patients.[55] Second-generation BTKis have addressed a number of these safety concerns and led to improvements in HRQoL as demonstrated by a recent quality-adjusted time without progression or toxicity (Q-TWiST) analysis which found that patients treated with second-generation BTKi had a longer time without disease progression and toxicity and shorter time with toxicity compared to patients treated with a first-generation BTKi or CIT.[46] As a next-generation BTKi, zanubrutinib, has the potential to address the safety and tolerability issues associated with first-generation BTKis or CIT in both previously untreated and R/R patients, and therefore, potentially improving patient HRQoL.[20,32]

B.1.3.3 Life expectancy

CLL progresses slowly and can be kept under control for many years with treatment. As described in Table 6, the majority of patients diagnosed with CLL in England remain alive at five years, with the five-year relative survival rate ranging from 95% for patients below 60 years, to 65% for those above 80 years.[47]

Table 6: Five-year survival rates for CLL across age groups in England in 2022

Age bracket	<60 years	60 – 69 years	70 – 79 years	≥ 80 years	All ages
5-year survival rate	95%	90%	80%	65%	85%

Source: The Haematological Malignancy Research Network[47]
CLL – Chronic lymphocytic leukaemia.

Survival is often dependent on patient age, disease stage and the presence or absence of high-risk mutations with many 'fit' patients expected to have a normal lifespan. In comparison, 'unfit' and high-risk patients often have reduced survival, as described in Table 7.[48] The introduction of targeted therapies has greatly improved survival in CLL as demonstrated in a recent study showing a statistically significant improvements in OS for second-generation BTKis compared with CIT in previously untreated patients with CLL at a 5-year follow-up (OS HR: 0.55; p=0.0474).[49]

Table 7: Proportion of patients surviving 5 years after diagnosis by risk level

Risk*	Proportion surviving ≥ 5 years after diagnosis
Low-risk	95%
Intermediate risk	80%
High-risk	65%
Very high-risk	25%

Source: Cancer Research UK[48] *An assessment of 'Risk' was based on 5 prognostic factors : age (>65), Binet stage (B or C), TP53 mutation (present), IGHV mutation (unmutated) and level of β_2 microglobulin in the blood.

B.1.3.4 Clinical pathway of care and place in therapy

The majority of patients with CLL have asymptomatic, early-stage disease at first (Binet stage A or B). These patients are usually managed with a 'Watch and Wait' approach, which involves blood count assessments and clinician examinations. Treatment is often only initiated once patients develop symptomatic, active disease. A large proportion of patients will never require any treatment for their disease over their lifetime, however, even with treatment, CLL remains incurable.[4]

The goal of CLL treatment is to effectively control disease whilst maintaining quality of life for patients. The optimal first-line treatment strategy is dependent on an increasing number of patient and cytogenetic factors, including age and fitness level, and the presence of high-risk mutations.[36] Treatment strategy is also influenced by patient- and clinician-choice.

A. Current treatments in previously untreated adults with CLL who are unsuitable for FCR and BR based therapy

Once a patient meets iwCLL criteria for treatment and exhibits active disease with symptoms (Binet stage C), the initial treatment choice in the first-line setting depends on a number of factors, including fitness level, age and the presence of high-risk features.[36] Patients who are 'unfit' are less likely to be suitable to undergo CIT with FCR or BR due to their toxicity profiles. Elderly patients are typically less 'fit' and more likely to present with comorbidities than younger patients, however some younger patients also have comorbidities that can impact ability to tolerate treatment and therefore are considered 'unfit'.[4,50]

As per the 2022 BSH guidelines, the main treatment options for patients without high-risk mutations who are considered 'unfit' for FCR and BR are acalabrutinib and venetoclax-obinutuzumab.[5] UK prescribing data for patients with CLL collected by IQVIA in December 2022, reported that in untreated patients who are considered unfit (defined as patients aged >65 or patient age ≤65 with comorbidities), [redacted]% are treated with BTKis. In contrast, only [redacted]% of unfit patients receive treatment with a venetoclax-based regimen.[7] These findings were supported by a quantitative survey and qualitative feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[8,9] Clinicians noted 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 syndrome and GI side effects. In comparison, acalabrutinib would typically be prescribed for

elderly patients or patients with comorbidities who would be unsuitable for fludarabine-based and bendamustine-based therapy.[10]

Whilst other treatments such as chlorambucil-obinutuzumab have been approved by NICE in this population, these treatments are no longer considered standard of care following the introduction of targeted therapies.[5] Further details can be found in Section B.1.1.1 Comparators.

B. Current treatments in previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable

High-risk prognostic factors, namely 17p deletion or TP53 mutation are predictive of aggressive disease and a poor response to CIT, and hence treatment choice is often driven by the presence of these genetic abnormalities.[51]

As per the 2022 BSH guidelines, the treatment choice in the first-line setting for high-risk patients is acalabrutinib, ibrutinib, or venetoclax-obinutuzumab, and is influenced by a number of factors including patient- and clinician-choice.[5,6] Whilst venetoclax-obinutuzumab is considered as an option in this population, the 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.[5] Since routine reimbursement by NICE, ibrutinib and acalabrutinib have therefore become established NHS care for the high-risk patient population.[7]

Feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company, supported that BTKis would typically be prescribed for patients with a 17p deletion or TP53 mutation 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 syndrome and GI side effects.[10] This was supported by UK prescribing data for patients with CLL collected by IQVIA in December 2022, in which [redacted]% of untreated patients with a 17p deletion or TP53 mutation were treated with a BTKi, and by a quantitative survey conducted by the Company.[7,8]

Whilst other treatments such as venetoclax monotherapy and idelalisib-rituximab have been approved by NICE in this population, these treatments are not considered standard of care and are rarely used.[5] Further details can be found in Section B.1.1.1 Comparators.

C. Current treatments in adults with R/R CLL who have had at least one previous therapy

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.[52]

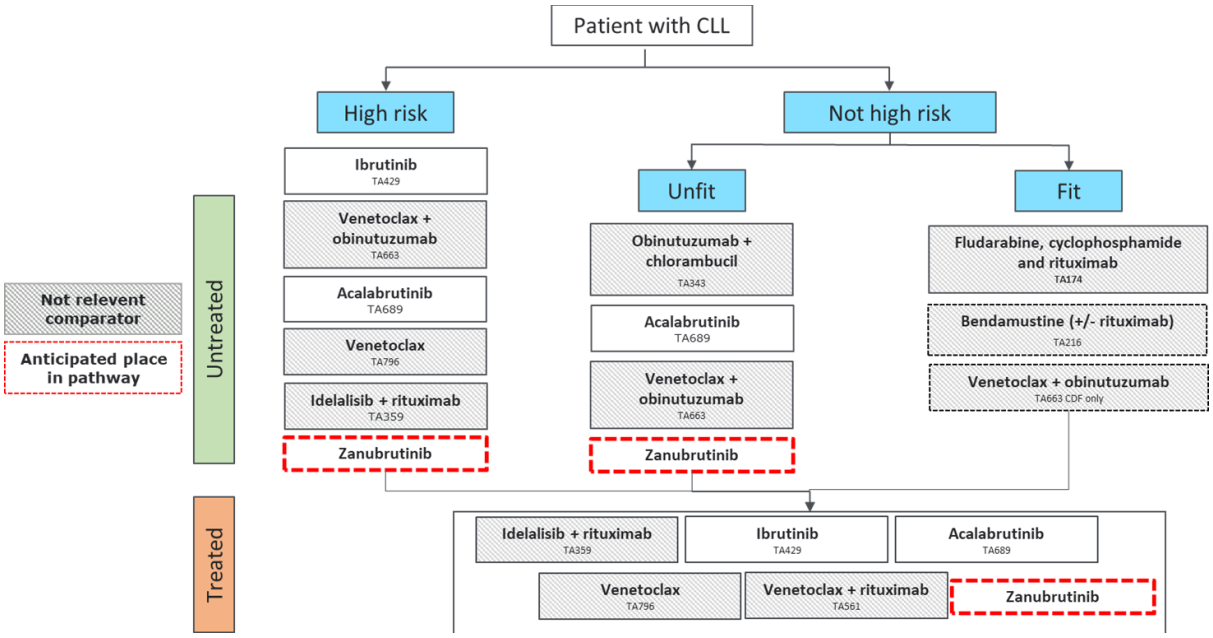
A 'sequencing' approach is recommended in the 2022 BSH guidelines which suggests that the optimal treatment following progression varies depending on the front-line therapy.[5] For patients progressing following front-line treatment with a BTKi, a BCL2i regimen is recommended and for patients progressing following front-line treatment with a BCL2i, a BTKi regimen is recommended. Whilst venetoclax-rituximab is recommended by NICE for treating R/R CLL, it is primarily used in patients previously treated with a BTKi.[19] Patients eligible for zanubrutinib are those who have not previously received treatment with BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial[20]), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib. This was confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[10] Furthermore, feedback gathered from UK experts at an advisory board (03 November 2022) conducted by the Company supported the sequencing concept in that patients previously treated with a BTKi would receive treatment with venetoclax-rituximab in the R/R setting.[11]

Whilst other treatments such as venetoclax monotherapy and idelalisib-rituximab have been approved by NICE in this population, these treatments are not considered standard of care and are rarely used.[5] Further details can be found in Section B.1.1.1 Comparators.

Zanubrutinib place in therapy in CLL

The proposed positioning of zanubrutinib in the clinical pathway is shown in Figure 1.

Figure 1: Clinical pathway of care and proposed positioning of zanubrutinib



CLL – Chronic lymphocytic leukaemia; TA – Technology appraisal.

It is anticipated that zanubrutinib will be used as a treatment for:

- Previously untreated patients with CLL who are unsuitable for FCR and BR therapy, i.e., patients considered 'unfit'.
- Previously untreated patients with CLL who have a 17p deletion or TP53 mutation in whom CIT is deemed unsuitable, i.e., patients considered 'high-risk'.
- Patients with R/R CLL who have had at least one previous therapy.

Zanubrutinib can be considered as an alternative BTKi for previously untreated patients, alongside acalabrutinib ('unfit' and high-risk' populations) and ibrutinib ('high-risk' population only). 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.[5] As zanubrutinib is a next-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. Furthermore, feedback gathered from UK experts at an advisory board (03 November 2022) conducted by the Company supported the positioning of zanubrutinib as an alternative BTKi treatment option.[11]

Zanubrutinib can be considered as an alternative BTKi in the R/R patient population, alongside acalabrutinib and ibrutinib. Whilst venetoclax-rituximab is recommended by NICE for treating R/R CLL, it is primarily used in patients previously treated with a BTKi.[19] Patients eligible for zanubrutinib are those who have not previously received treatment with a BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial[20]), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib. Furthermore, feedback gathered from UK experts at an advisory board (03 November 2022) conducted by the Company supported the positioning of zanubrutinib as an alternative BTKi treatment option in this patient population, with experts agreeing with the treatment sequencing concept.[11]

B.1.3.5 Clinical guidelines

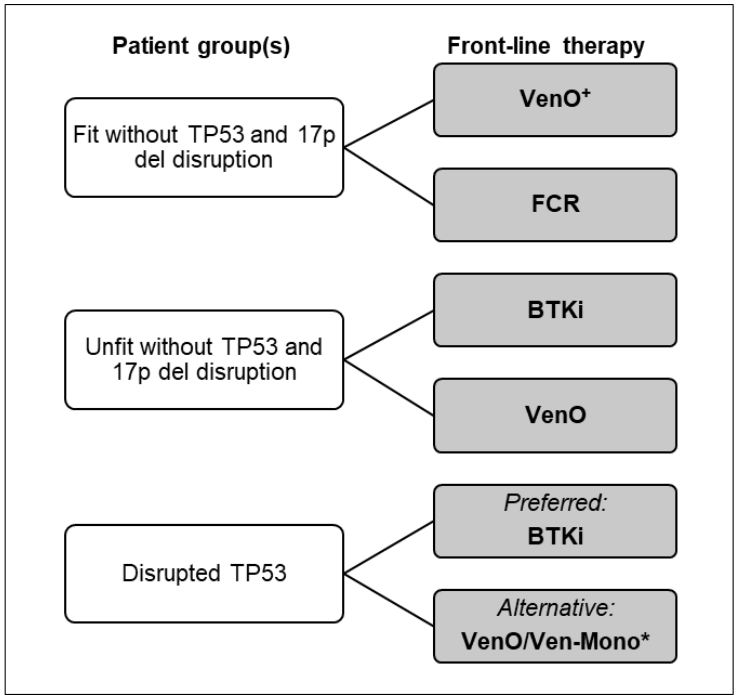
B.1.3.5.1 Guidelines – first-line treatment

The 2022 BSH guidelines recommend that:

- In the 'fit' population without a TP53 disruption, FCR remains a viable option however prospective data shows the use of venetoclax-obinutuzumab may be equally effective in fit patients.
- In the 'unfit' population, venetoclax-obinutuzumab and acalabrutinib are recommended options as initial therapy in patients unsuitable for CIT irrespective of TP53 status. However, UK prescribing data for patients with CLL collected by IQVIA in December 2022 reported low venetoclax-obinutuzumab usage in this population and that the majority of patients ([redacted]%) are treated with BTKis.[7] Clinician feedback supports that venetoclax-obinutuzumab would be more frequently used for 'fit' patients, whilst BTKis are reserved for less 'fit' patients.[10]
- In the TP53 disrupted population, acalabrutinib and ibrutinib are the preferred options whilst venetoclax-obinutuzumab or venetoclax monotherapy are alternative therapy options. However, UK prescribing data for patients with CLL collected by IQVIA in December 2022 reported low usage of venetoclax-based regimens in this population and that the majority of patients ([redacted]%) are treated with BTKis.[7]
- Bendamustine-based and chlorambucil-based CIT regimens are no longer recommended for first-line treatment of CLL and account for [redacted]% of the market share for patients with untreated CLL, based on UK prescribing data for patients with CLL collected by IQVIA in December 2022.[7]

Figure 2 summarises the guidance for first-line (untreated) management of patients with CLL published by the BSH.[5]

Figure 2: Summarised 2022 BSH guidance diagram for untreated CLL



+Venetoclax-Obinutuzumab is available for NHSE patients on the CDF for this patient population and is preferred over FCR *Only a first-line option for TP53 disrupted patients who are ineligible for BTKi. *Source: BSH* 2022[5]
BSH – British Society of Haematology; BTKi – Bruton tyrosine kinase inhibitor; CLL – chronic lymphocytic leukaemia; FCR – fludarabine-cyclophosphamide-rituximab; Ven-Mono – Venetoclax monotherapy; VenO – Venetoclax-Obinutuzumab.

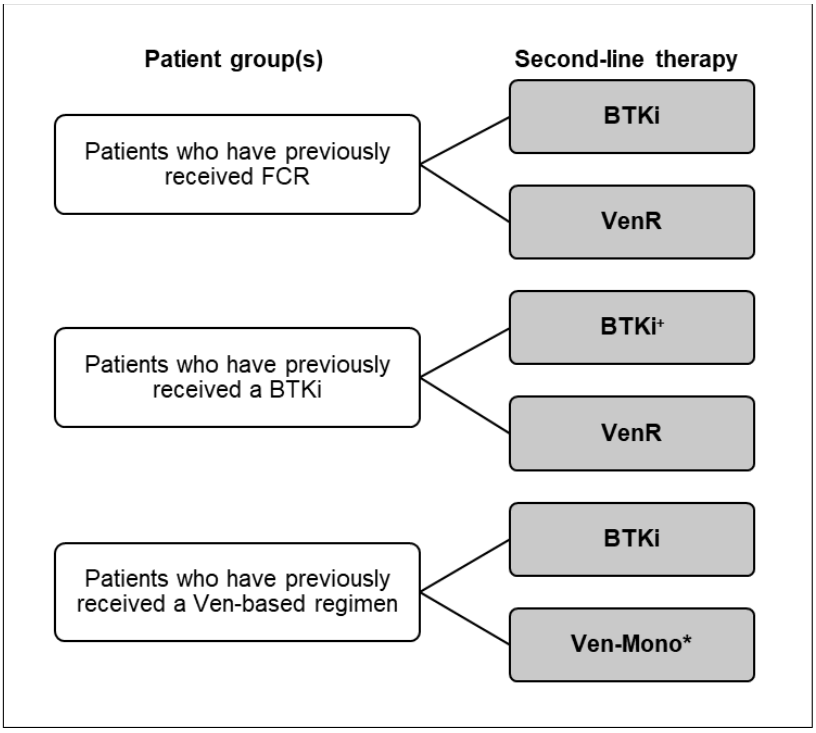
B.1.3.5.2 Guidelines – R/R treatment

The 2022 BSH guidelines recommend a treatment sequencing approach, stating that:

- Acalabrutinib, ibrutinib, venetoclax-rituximab and venetoclax monotherapy are the treatments of choice for relapsed CLL.
- Venetoclax-rituximab or venetoclax monotherapy should be offered for patients relapsing after BTKi, irrespective of TP53 status.
- A BTKi should be offered for patients relapsing following fixed-duration venetoclax-based therapy. Alternatively, patients can be retreated with venetoclax depending on the duration patients were progression-free in first-line. However, the guidelines also note that evidence for this approach is limited.
- Idelalisib-rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment.

Whilst the guidelines for R/R CLL state that individualised decisions taking into account patient preference and toxicity profile are recommended, a 'sequencing' approach is considered in order to select the optimal strategy for patients relapsing following treatment with front-line targeted treatments. For patients progressing following front-line treatment with a BTKi, a BCL2i regimen is recommended. For patients progressing following front-line treatment with a BCL2i regimen, a BTKi treatment is preferred. Feedback gathered at an advisory board (03 November 2022), confirmed that a 'sequencing' approach is used when selecting a second-line treatment option.[11] Figure 3 presents the 2022 BSH guidelines for patients with R/R CLL.

Figure 3: Summarised 2022 BSH guidance diagram for R/R CLL



+Alternate BTKi can be offered as an option if intolerant to initial BTKi choice *Venetoclax monotherapy can be offered to patients relapsing after fixed-duration Venetoclax-based regimens.
Source: BSH 2022[5]
BSH – British Society of Haematology; BTKi – Bruton tyrosine kinase inhibitor; CLL – chronic lymphocytic leukaemia; FCR – fludarabine-cyclophosphamide-rituximab; R/R – relapsed refractory; Ven-Mono – Venetoclax monotherapy; VenR – Venetoclax-Rituximab.

B.1.3.6 Unmet need

CLL remains to be an uncurable disease and patients suffering have a median OS of 9 years.[34,53] Many patients with CLL relapse following initial treatment and/or have refractory disease and as CLL is a chronic disease, multiple lines of therapy, often with different

mechanisms of action, are needed. As such, the introduction of alternative therapies, like zanubrutinib, into the treatment pathway is desirable as they can delay progression and provide an alternative treatment option for patients with CLL.

CIT regimens have limitations in their use in CLL and are no longer considered standard of care. In addition, patients with high-risk genetic profile, such as 17p deletion or TP53 mutation, typically respond poorly to CIT.[54] The introduction of targeted therapies such as BTKis and BCL-2is have caused a paradigm shift in the treatment of CLL, and provided chemotherapy-free options with high efficacy. The therapies available to CLL patients differ in their safety profiles, allowed comedications, and administration procedures, which are taken into account when deciding on the best course of treatment.

Specifically, BTKis have transformed CLL management due to high efficacy and consistent responses irrespective of mutational status.[49,55–57] However, first-generation BTKis such as ibrutinib, have imperfect target specificity and are associated with tolerability issues.[55] Cardiac adverse events (AEs), such as atrial fibrillation/flutter, can be a substantial limiting factor of BTKi treatment. An increased rate of atrial fibrillation was reported with ibrutinib versus CIT treatment in randomised studies.[57,58] Tolerability issues and high rates of AEs lead to high rates of discontinuation of ibrutinib and limit its use in patients with cardiac comorbidities.

Although second-generation BTKis such as acalabrutinib have addressed some of these safety concerns, there is still a need for new, well tolerated treatment options. An ongoing, phase 2, single-arm trial is evaluating the efficacy of zanubrutinib in 67 patients previously treated for B-cell malignancies who became intolerant to ibrutinib, acalabrutinib, or both. The most common intolerance events reported were fatigue and hypertension for ibrutinib, and arthralgia and myalgia for acalabrutinib. Results at a median follow-up time of 12 months demonstrated that the majority of intolerance events (70% for ibrutinib and 83% for acalabrutinib) did not recur with zanubrutinib, and that no events recurred with higher severity.[59] Furthermore, AEs associated with zanubrutinib seemed more tolerable and manageable for patients than those associated with other BTKis.[59] This suggests that zanubrutinib, as a next-generation BTKi, is associated with improved tolerance and safety when compared to first-generation and second-generation BTKis and has the potential to reduce the rate of discontinuation due to intolerance events.

Zanubrutinib is a simple oral regimen and does not require frequent hospital visits. Furthermore, zanubrutinib is a next-generation BTKi with less off-target effects and improved pharmacological properties with greater selectivity, resulting in sustained disease control and an improved safety and tolerability profile compared to existing BTKi therapies. Zanubrutinib will therefore be a welcomed treatment option for patients with CLL.

B.1.4 Equality considerations

Due to the lack of clinical trial data available for patients with untreated CLL for which FCR or BR is suitable ('fit'), the Company has not presented an assessment in this population. As such, an equality issue arises in that younger and fitter patients are denied access to a new treatment option that is efficacious, well-tolerated and improves patient choice, which is crucial given the heterogeneity of CLL and varying levels of response to treatment. The inequality of a BTKi being made available only in 'unfit' or 'high-risk' patients with untreated CLL was highlighted by UK patient representatives in previous NICE appraisals as well as by patient and clinician groups that the Company has engaged with during this submission process.[4,6]

Currently, the only treatment options routinely reimbursed by NICE for 'fit' patients are FCR and BR with venetoclax-obinutuzumab only available via the Cancer Drugs Fund (CDF). Whilst CIT was previously considered standard of care and can produce durable responses, it is associated with high rates of AEs, a risk of secondary myeloid cancers and significant HRQoL issues and usage has declined as confirmed by UK clinical experts.[5,8,9,11,60–65] In addition, following the COVID-19 pandemic, the use of CIT has further declined to avoid unnecessary hospital visits. Though the approval of venetoclax-obinutuzumab via the CDF has introduced a targeted chemotherapy-free option for 'fit' patients, there is still a clear unmet need for new mechanisms of actions that offer improved clinical outcomes in this population, as highlighted by feedback gathered from UK experts at an advisory board (03 November 2022) conducted by the Company.[11] Furthermore, UK patient representatives in previous NICE appraisals as well as through the Company's engagement have emphasised the need for a range of treatment options for patients with CLL given the heterogeneity of both the disease and patient population and in particular, the need for non-CIT treatment options.[4] This is supported by UK prescription data gathered by the Company that shows that despite the availability of venetoclax-obinutuzumab via the CDF, up to [redacted]% of 'fit' patients are prescribed a BTKi, further highlighting the need for additional treatment options

in this population. In addition, there appears to be a preference for single agents in first-line rather than combination therapies to avoid the risk of developing double refractory disease early to the major treatment classes in CLL.[66]

Clinical expert opinion suggests that zanubrutinib is likely to be as clinically effective in this population as in previously untreated unfit or high-risk CLL.[11] The FLAIR and E1912 studies comparing first-generation BTKi with FCR demonstrated that ibrutinib-rituximab was associated with statistically significantly improved PFS, at least comparable OS (OS was statistically significantly improved in E1912), and an increased time to subsequent treatment.[58,67] Although all the ibrutinib-treated patients in the FLAIR and E1912 trials also received rituximab, the benefits of combining rituximab with ibrutinib are unclear. Previous trials have shown no differences in PFS or OS between ibrutinib-alone and ibrutinib–rituximab groups in CLL.[58,67] Given the superiority of zanubrutinib over BR in SEQUOIA and over ibrutinib in ALPINE, feedback gathered from UK clinical experts at an advisory board (03 November 2022) conducted by the Company noted that it is plausible to hypothesise that zanubrutinib might at least produce similar results as seen with first-generation BTKis in the FLAIR and E1912 trials.[11]

Whilst a cost-effectiveness assessment in the 'fit' population has not been provided due to lack of clinical trial data in this population, given that the cost-effectiveness of zanubrutinib versus BR was confirmed in NICE TA833 for Waldenstrom's macroglobulinaemia (WM), with the current PAS, it is plausible to assume that zanubrutinib would also be cost-effective versus FCR (the most relevant comparator) in this population.[68]

As there are no ongoing clinical trials or data collection plans comparing zanubrutinib with CIT in 'fit' patients, zanubrutinib is not considered a candidate for the CDF in this population.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify RCTs investigating treatments in patients with previously untreated and R/R CLL. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated are presented in Appendix D.

The SLR conducted was broader than the scope of this submission and as such, studies were only extracted if they included zanubrutinib, acalabrutinib or ibrutinib, as the treatments of interest for this appraisal (Section B1).

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified two RCTs in untreated CLL and three RCTs in R/R CLL which evaluate either zanubrutinib or one of the comparators of interest, with details provided in Table 8.

Table 8: Summary of study characteristics for RCTs identified in the SLR

Publication source (author_year)	Trial name(if any)	Treatment/Group	Publication type	Study setting	Study phase
Untreated CLL					
Tam (2021)[69]	SEQUOIA (NCT03336333)	**Cohort 1:** **Treatment arm A:** Zanubrutinib (n=241) **Treatment arm B:** Bendamustine + Rituximab (n=238) **Cohort 2:** **Treatment arm C:** Zanubrutinib (n=111)	Journal article	Multicentre	III
Sharman (2019)[70]	ELEVATE-TN (NCT02475681)	**Treatment arm 1:** Acalabrutinib plus obinutuzumab (n=179) **Treatment arm 2:** Acalabrutinib (n=179) **Treatment arm 3:** Obinutuzumab plus chlorambucil (n=177)	Journal article	Multicentre	III
R/R CLL					
Hillmen (2021)[71]	ALPINE (NCT03734016)	**Treatment arm 1:** Zanubrutinib (n=207)	Journal article	Multicentre	III

Publication source (author_year)	Trial name(if any)	Treatment/Group	Publication type	Study setting	Study phase
		Treatment arm 2: Ibrutinib (n=208)			
Hillmen (2021)[72]	ELEVATE-RR (NCT02477696)	**Treatment arm 1:** Acalabrutinib (n=268) **Treatment arm 2:** Ibrutinib (n=265)	Journal article	Multicentre	III
Ghia (2019)[73]	ASCEND (NCT02970318)	**Treatment arm 1:** Acalabrutinib (n=155) **Treatment arm 2:** Rituximab plus idelalisib (n=119) **Treatment arm 3:** Bendamustine plus rituximab (n=36)	Journal article	Multicentre	III

RCT – Randomised controlled trial; SLR – systematic literature review.

Zanubrutinib has been studied in a comprehensive clinical development programme, including two pivotal phase III studies which have been conducted in previously untreated and R/R CLL. The SEQUOIA (NCT03336333) study provides comprehensive efficacy and safety data to evaluate zanubrutinib versus BR in patients with previously untreated CLL.[32] The ALPINE (NCT03734016) study provides comprehensive efficacy and safety data to evaluate zanubrutinib versus ibrutinib in patients with R/R CLL/SLL.[74] A summary of the ALPINE and SEQUOIA studies is provided in Table 9.

Table 9: Clinical effectiveness evidence

Study	SEQUOIA (BGB-3111-304; NCT03336333)	ALPINE (BGB-3111; NCT03734016)
Study design	Phase 3, open label, randomised, multicentre study	Phase 3, open label, randomised, multicentre study
Population	Patients with a diagnosis of CD20-positive CLL or SLL that met the iwCLL criteria, no prior treatment, age ≥ 65 years, or age 19–64 years with a creatinine clearance below 70 mL/min, history of previous serious infection or multiple infections in the past 2 years and/or a CIRS score > 6	Patients ≥18 years with a diagnosis of CLL/SLL that met the iwCLL criteria, relapsed or refractory to at least one prior systemic therapy for CLL/SLL
Intervention(s)*	Zanubrutinib	Zanubrutinib
Comparator(s)	Bendamustine-rituximab	Ibrutinib
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	NA	NA
Reported outcomes specified in the decision problem	**PFS**, ORR, OS, TTTF, **AEs**, **HRQoL**	ORR, **PFS**, **OS**, TTTF, **AEs**, **HRQoL**
All other reported outcomes	Pharmacokinetics, DOR, medical resource utilisation	Pharmacokinetics, DOR, MRD

AEs – Adverse events; CIRS – Cumulative Illness Rating Scale; CLL – Chronic lymphocytic leukaemia; DOR – Duration of response; HRQoL – Health-related quality of life; MRD – Minimal residual disease; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; SLL – Small lymphocytic lymphoma; TTTF – Time-to-treatment failure.
*Zanubrutinib-venetoclax is also an intervention within the SEQUOIA trial protocol, however the focus of this appraisal is zanubrutinib monotherapy (aligned with the licensed indication for zanubrutinib in CLL). Outcomes in **bold** are used in the economic model.
Source: SEQUOIA CSR[75], ALPINE CSR[76]

B.2a.3 Summary of methodology of the relevant clinical effectiveness evidence: previously untreated CLL

B.2a.3.1 Study design

SEQUOIA is an international, randomised, open-label, multi-centre, phase 3 trial of zanubrutinib versus BR in patients with previously untreated CLL. The study was designed in four cohorts:

- **Cohort 1**: patients without del(17p) randomised to receive either zanubrutinib (arm A) or BR (arm B)
- **Cohort 1a**: only Chinese patients without del(17p) randomised to receive either zanubrutinib or BR (opened for enrolment in China when the Cohort 1 sample size had been reached)
- **Cohort 2**: patients with del(17p) who received zanubrutinib (arm C)
- **Cohort 3**: patients with del(17p)/TP53mut who received zanubrutinib in combination with venetoclax (arm D)

As Cohort 1a was comprised only of Chinese patients, the demographics were not deemed representative of the UK population and as such, discussion on Cohort 1a have been omitted from the submission. In addition, as Cohort 3 is an exploratory arm assessing the outcomes of zanubrutinib in combination with venetoclax, the study cohort was not deemed relevant to the decision problem. Furthermore, Cohort 3 is still ongoing as of the latest data cut-off and results have not yet read out. As such, only Cohorts 1 and 2 are deemed relevant to the submission and will be discussed henceforth.[75]

In Cohort 1, a total of 479 patients were randomised 1:1 between zanubrutinib and BR, with randomisation stratified by age (< 65 years versus ≥ 65 years), Binet stage (C versus A or B), IGHV mutational status (mutated versus unmutated), and geographic region (North America versus Europe versus Asia-Pacific). Patients in Arm B of Cohort 1 were allowed to cross over to zanubrutinib at the time of disease progression as confirmed by independent central review (IRC).[75]

In Cohort 2, a total of 111 patients were enrolled and allocated to receive treatment with zanubrutinib and this treatment arm is among the largest bodies of prospective evidence collected specifically for patients with a 17p deletion. Patients in Cohort 2 were not

randomised to BR as this patient population has poor clinical outcomes and poor response to CIT. A total of 65 patients in SEQUOIA were recruited from UK sites.[75]

The primary trial endpoint was IRC-assessed PFS in Cohort 1 and the key secondary endpoint was IRC-assessed ORR in Cohort 2.[75]

Table 10 summarises the SEQUOIA trial methodology. Study design and randomisation is presented in Figure 4.

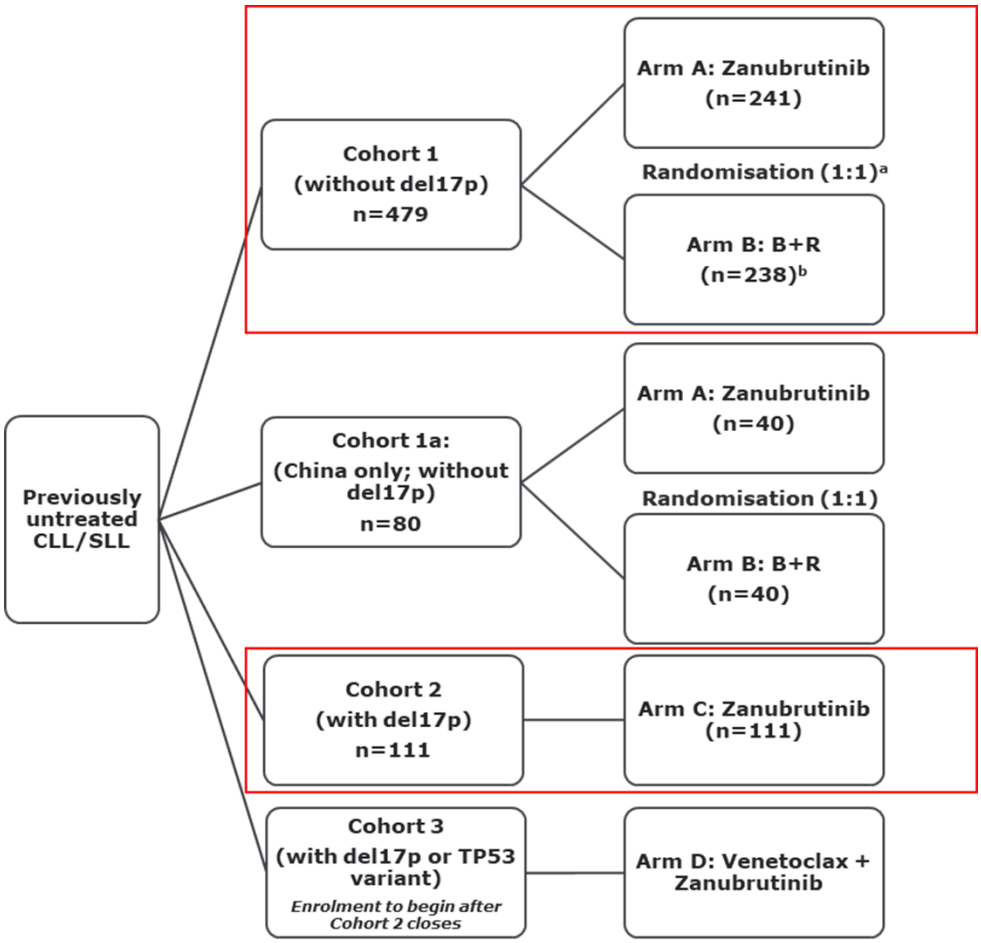
Table 10: Summary of trial methodology

Study details	SEQUOIA (BGB-3111-304; NCT03336333)
Location	Australia, Austria, Belgium, Czechia, France, Italy, New Zealand, Poland, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, United States
Design	Phase 3, open label, randomised, multi-centre study in participants with previously untreated CLL or SLL who were deemed ineligible for FCR therapy. Ineligible for FCR was defined as: ≥ 65 years of age at the time of informed consent, OR 18 to 64 years of age and must have had 1 or more of the following factors: • Cumulative Illness Rating Scale (CIRS) score > 6 ○ A CIRS was not required; it could have been used to meet this inclusion requirement. • Creatinine clearance < 70 mL/min • History of previous serious infection or multiple infections in the past 2 years
Randomisation	Patients were stratified into one four cohorts depending on mutation status (only Cohorts 1 and 2 are relevant for this submission): <u>Cohort 1 (without del17p):</u> • Arm A: zanubrutinib • Arm B: bendamustine-rituximab <u>Cohort 1a (China only; without del17p):</u> • Arm A: zanubrutinib • Arm B: bendamustine-rituximab <u>Cohort 2 (with del17p):</u> • Arm C: zanubrutinib <u>Cohort 3 (with del17p or pathogenic TP53 variant):</u> • Arm D: zanubrutinib-venetoclax For patients in Cohort 1/1a, IRT was used to randomise patients 1:1 to either zanubrutinib or bendamustine-rituximab. Randomisation was stratified by age (< 65 years versus ≥ 65 years), Binet stage (C versus A or B), IGHV mutational status (mutated versus unmutated), and geographic region (North America versus Europe versus Asia-Pacific). As Cohort 1a only enrolled patients from Chinese sites, geographic region was not a randomisation stratification factor in this cohort. Cohorts 2 and 3 were single arm cohorts and as such, were non-randomised.
Blinding	This was an open-label study; however, the IRC for response assessment was blinded to study treatment.

Study details	SEQUOIA (BGB-3111-304; NCT03336333)
	Whilst the independent DMC was not blinded due to the open-label nature of the study, the sponsor did not have access to aggregated data summaries by actual study treatment assignment while the study was ongoing to avoid unwanted bias.
Treatment	Cohort 1 (without del17p) • Arm A (zanubrutinib) o Oral zanubrutinib 160 mg twice a day (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression. • Arm B (bendamustine-rituximab) o IV bendamustine over six cycles, 90 mg/m^2/day on the first two days of each cycle. o IV rituximab over six cycles, 375 mg/m^2 on Day 0 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 to 6. • Crossover from Arm B o Oral zanubrutinib 160 mg twice a day (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression. Cohort 2 (with del17p) • Arm C (zanubrutinib) o Oral zanubrutinib 160 mg twice a day (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression.
Endpoints	Primary endpoint: • PFS (IRC) in Cohort 1 Secondary endpoints: • ORR (IRC and INV) in Cohort 1 • OS in Cohort 1 • DOR (IRC and INV) in Cohort 1 • PFS (INV) in Cohort 1 • PROs (EORTC QLQ-C30, EQ-5D-5L) in Cohort 1 • ORR (IRC and INV) in Cohort 2 • PFS (IRC and INV) in Cohort 2 • DOR (IRC and INV) in Cohort 2 • Safety parameters in Cohort 1 and 2 • Pharmacokinetic parameters in Cohort 1 (arm A only) and Cohort 2
Subgroup analysis	Age, sex, race, geographic region, cancer type (CLL versus SLL), Binet stage, ECOG, bulky disease, IGHV mutational status, LDH, cytopenia, 11q deletion, 13q deletion, complex karyotype, trisomy 12, TP53 mutation, serum β_2 microglobulin

CLL – Chronic lymphocytic leukaemia; del17p – 17p deletion; DMC – Data Monitoring Committee; DOR – Duration of response; ECOG – European Cooperative Oncology Group; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D – 5-dimension EuroQol questionnaire; FCR – fludarabine-cyclophosphamide-rituximab; IGHV – immunoglobulin heavy chain gene; INV – investigator assessed; IRC – independent central review; IRT – Interactive Response Technology; IV – intravenous; LDH – Lactate dehydrogenase; mg – milligram; PFS – Progression-free survival; PRO – Patient reported outcome; ORR – Overall response rate; OS – Overall survival; SLL – Small lymphocytic lymphoma.
Source: SEQUOIA CSR[75]

Figure 4: SEQUOIA study schematic



CLL – Chronic lymphocytic leukaemia; SLL – Small lymphocytic lymphoma. Red box = cohorts relevant to this submission.
[a] Randomisation for Cohort 1 was stratified by age (< 65 years versus ≥ 65 years), Binet stage (C vs A or B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia Pacific).
[b] Crossover for patients in Arm B to receive next-line zanubrutinib is allowed after disease progression as confirmed by IRC.
Source: SEQUOIA CSR[75]

B.2a.3.2 Eligibility criteria

Eligible patients were aged ≥65 years or, if 18-64 years, had a creatinine clearance below 70 mL/min, history of previous serious infection or multiple infections in the past 2 years and/or a CIRS score > 6, meaning that patients were unsuitable for treatment with FCR-based therapy. Key inclusion and exclusion criteria for the SEQUOIA trial are presented in Table 11.[75]

Table 11: Key eligibility criteria for SEQUOIA

Key inclusion criteria

• Unsuitable for treatment with FCR defined as ≥ 65 years of age at the time of informed consent, OR 18-64 years of age and must have had 1 or more of the following factors:
  ○ CIRS score > 6
  ▪ A baseline CIRS score was not required for enrolment in the trial, however if the CIRS score was available, it could have been used to assess eligibility for the trial
  ○ Creatinine clearance < 70 mL/min
  ○ History of previous serious infection or multiple infections in the past 2 years
• Confirmed diagnosis of CD20-positive CLL or SLL that met the iwCLL criteria[27] and requiring treatment as defined by specific criteria
• Measurable disease by CT/MRI, with measurable disease defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters
• CLL/SLL requiring treatment based on at least 1 of the iwCLL criteria[27]
• ECOG performance status of 0, 1 or 2
• Life expectancy ≥ 6 months
• Adequate bone marrow and organ function by specific criteria
• FISH results from the study-specified central laboratory confirming the presence or absence of del(17p)

Key exclusion criteria
• Previous systemic treatment for CLL/SLL • Required ongoing need for corticosteroid treatment • Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation • Clinically significant cardiovascular disease • Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast, or localised Gleason score 6 prostate cancer • History of severe bleeding disorder, or history of spontaneous bleeding requiring blood transfusion or other medical intervention • History of stroke or intracranial haemorrhage within 6 months before first dose of study drug • Severe or debilitating pulmonary disease • Active fungal, bacterial, and/or viral infection requiring systemic therapy • Known central nervous system involvement by leukaemia or lymphoma • Vaccination with a live vaccine within 35 days prior to the first dose of study drug

CIRS – Cumulative illness rating scale; CLL – Chronic lymphocytic leukaemia; CT – Computerised tomography; ECOG – Eastern Cooperative Oncology Group; FCR – Fludarabine-cyclophosphamide-rituximab; FISH – Fluorescence in situ hybridisation; iwCLL– International Workshop on Chronic Lymphocytic Leukaemia; MRI – Magnetic resonance imaging; SLL – Small lymphocytic lymphoma.
Source: SEQUOIA CSR[75]

B.2a.3.3 Outcome measures

The definitions of the outcome measures available in the SEQUOIA trial and whether they are used in the economic model are presented in Table 12. Only data from Cohort 1 and Cohort 2 are used within the economic model.

Table 12: Outcome measures available from SEQUOIA

Endpoint	Definition	Datacut available*	Used in economic model
Primary			

Endpoint	Definition	Datacut available*	Used in economic model
PFS (IRC)	Time from randomisation to the date of first documentation of IRC-assessed disease progression or death due to any cause, whichever occurs first, using the iwCLL guidelines[27] with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL)	07 May 2021	Yes
Secondary			
PFS (INV)	Time from randomisation to the date of first documentation of INV-assessed disease progression or death due to any cause, whichever occurs first, using the iwCLL guidelines[27] with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL)	07 May 2021	Yes
ORR (IRC and INV)	The proportion of patients achieving a best overall response of CR, CRi, nPR, PR or PRL at or before initiation of subsequent anti-cancer therapy as determined by IRC or INV assessment	07 May 2021	No
OS	Time from randomisation to the date of death due to any reason	07 March 2022	No
DOR (IRC and INV)	Time from the date that criteria for response (i.e., PRL or better) are first met to the date that disease progression is objectively documented or death, whichever occurs first, as determined by IRC or INV assessment using the iwCLL criteria with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL)	07 May 2021	No
HRQoL (EORTC QLQ-C30, EQ-5D-5L)	Change from baseline in EORTC QLQ-C30 and EQ-5D-5L scores	07 May 2021	Yes (scenario analysis only)

Endpoint	Definition	Datacut available*	Used in economic model
Safety	AEs classified based on MedDRA (Version 24.0) and graded according to the NCI-CTCAE (version 4.03)	07 May 2021	Yes

CR – Complete response; CRi – Complete response with incomplete bone marrow recovery; CTCAE – Common Terminology Criteria for Adverse Events; DOR – Duration of response; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer Core Quality of Life; EQ-5D – Euroqol 5-Dimensions; HRQoL – Health-related quality of life; iwCLL – International Workshop on Chronic Lymphocytic Leukaemia; NHL – non-Hodgkin lymphoma; nPR – nodular partial remission; ORR – Overall response rate; OS – Overall survival; PR – Partial response; PRL – Partial response with lymphocytosis; SD – Stable disease.
*Median follow-up for 07 May 2021 data-cut: 26.35 months for Arm A, 25.92 months for Arm B (Cohort 1) and 30.52 months for Arm C (Cohort 2). Median follow-up for 07 March 2022 data-cut: 36.1 months for Arm A, 35.4 months for Arm B (Cohort 1).
Source: SEQUOIA CSR[75]

B.2a.3.4 Patient characteristics

Cohort 1

Demographic and baseline characteristics were generally balanced between the zanubrutinib arm and BR arm in the intention to treat (ITT) Analysis Set in Cohort 1 as presented in Table 13.

However, small differences were seen in race and age. The zanubrutinib arm had a slightly higher proportion of white patients (91.7%) compared with the BR arm (86.6%). The median age was 70 years in both arms and the proportion of patients of ≥ 65 years in the zanubrutinib arm (81.3%) was comparable to that in the BR arm (80.7%). However, the zanubrutinib arm had a slightly higher proportion of patients of ≥ 75 years (26.1%) compared with the BR arm (22.3%). Most patients were randomised at sites in Europe (72.2% in the zanubrutinib arm; 72.3% in the BR arm), and most patients in both arms had an ECOG performance status (PS) of 0 or 1 (93.8% in the zanubrutinib arm; 91.6% in the BR arm).[75]

A small proportion of patients recruited in Cohort 1 had del17p or TP53 mutations (7.1% in the zanubrutinib arm and 5.5% in the BR arm). These patients were inadvertently allocated to Cohort 1 prior to mutation screening. Since this is only a small proportion of patients, and the proportion is balanced across arms, this is unlikely to impact study outcomes.[75]

Table 13: Demographics and baseline characteristics in SEQUOIA Cohort 1

	BR (N = 238)	Zanubrutinib (N = 241)
Cancer type, n (%)		
CLL	218 (91.6)	221 (91.7)
SLL	20 (8.4)	20 (8.3)

	BR (N = 238)	Zanubrutinib (N = 241)
Age (years)		
Mean (SD)	69.35 (7.391)	69.82 (7.74)
Median	70	70
< 65 years	46 (19.3)	45 (18.7)
≥ 65 and < 75 years	139 (58.4)	133 (55.2)
≥ 75 years	53 (22.3)	63 (26.1)
Sex, n (%)		
Male	144 (60.5)	154 (63.9)
Female	94 (39.5)	87 (36.1)
White	206 (86.6)	221 (91.7)
Not Reported	21 (8.8)	9 (3.7)
Asian	9 (3.8)	4 (1.7)
Black or African American	1 (0.4)	4 (1.7)
Unknown	1 (0.4)	2 (0.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)
Geographic Region, n (%)		
Europe	172 (72.3)	174 (72.2)
Asia Pacific[a]	38 (16.0)	33 (13.7)
North America	28 (11.8)	34 (14.1)
ECOG Performance Status, n (%)		
0	101 (42.4)	110 (45.6)
1	117 (49.2)	116 (48.1)
2	20 (8.4)	15 (6.2)
Time from initial diagnosis of CLL/SLL to randomisation (months)		
Mean (SD)	38.64 (38.60)	47.62 (49.67)
Median	28.67	31.28
Binet stage at study entry for CLL, n (%)		
A	28 (12.8)	30 (13.6)
B	124 (56.9)	126 (57.0)
C	66 (30.3)	65 (29.4)
Del17p, n (%)		
Yes	0 (0.0)	2 (0.8)*
No	238 (100.0)	239 (99.2)
TP53 mutation, n (%)		
Yes	13 (5.5)	15 (6.2)
No	210 (88.2)	217 (90.0)

	BR (N = 238)	Zanubrutinib (N = 241)
Missing	15 (6.3)	9 (3.7)
Del17p or TP53 mutation, n (%)		
Yes	13 (5.5)	17 (7.1)
No	225 (94.5)	224 (92.9)
IGHV mutational status, n (%)		
Mutated	110 (46.2)	109 (45.2)
Unmutated	121 (50.8)	125 (51.9)
Undetermined	7 (3.0)	7 (2.9)
β_2 microglobulin, n (%)		
Mean (SD)	4.97 (6.94)	4.49 (3.19)
≤ 3.5 mg/L	98 (41.2)	99 (41.1)
> 3.5 mg/L	131 (55.0)	135 (56.0)

BR – Bendamustine-rituximab; CLL – chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; IGHV – Immunoglobulin heavy chain variable region; PS – Performance status; SD – Standard deviation; SLL – Small lymphocytic lymphoma.
[a] Asia Pacific: Australia; New Zealand; Korea; China; and Taiwan, China.
*Inadvertent inclusion of these patients in Arm A.
Source: SEQUOIA CSR[75]

Cohort 2

Demographic and baseline characteristics for zanubrutinib in the Safety Analysis Set in Cohort 2 is presented in Table 14. The demographic and baseline characteristics were generally well-balanced between zanubrutinib in Cohort 1 and Cohort 2, with the exception of geographic region and mutation status. Of note, there were more patients enrolled from Asia Pacific region in the zanubrutinib arm in Cohort 2 (42.3%), compared with the zanubrutinib arm in Cohort 1 (13.7%). The majority of the patients enrolled in the Asia Pacific region were from Australia/New Zealand (>90% across Cohort 1 and 2).[75]

Table 14: SEQUOIA: demographics and baseline characteristics in Cohort 2

	Zanubrutinib (N=111)
Cancer type, n (%)	
CLL	100 (90.1)
SLL	11 (9.9)
Age (years)	
Mean (SD)	69.77 (7.75)
Median	70.00
< 65 years	16 (14.4)

	Zanubrutinib (N=111)
≥ 65 and < 75 years	68 (61.3)
≥ 75 years	27 (24.3)
Sex, n (%)	
Male	79 (71.2)
Female	32 (28.8)
Race, n (%)	
White	105 (94.6)
Not Reported	4 (3.6)
Asian	1 (0.9)
Unknown	1 (0.9)
Black or African American	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Geographic region, n (%)	
Europe	52 (46.8)
Asia Pacific [a]	47 (42.3)
North America	12 (10.8)
ECOG Performance Status, n (%)	
0	44 (39.6)
1	53 (47.7)
2	14 (12.6)
Time from initial diagnosis of CLL/SLL to randomization (month)	
Mean (SD)	40.54 (55.33)
Median	21.39
Binet stage at study entry for CLL, n (%)	
A	14 (14.0)
B	49 (49.0)
C	37 (37.0)
Del17p, n (%)	
Yes	110 (99.1)*
No	1 (0.9)
TP53 mutation, n (%)	
Yes	47 (42.3)
No	62 (55.9)
Missing	2 (1.8)
Del17p and/or TP53 mutation, n (%)	
Yes	110 (99.1)

	Zanubrutinib (N=111)
No	1 (0.9)
IGHV mutational status, n (%)	
Mutated	36 (32.4)
Unmutated	67 (60.4)
Undetermined	8 (7.2)
β_2 microglobulin, n (%)	
Mean (SD)	5.16 (2.20)
≤ 3.5 mg/L	23 (20.7)
> 3.5 mg/L	78 (70.3)

CLL – chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; IGHV – Immunoglobulin heavy chain variable region; SD – Standard deviation; SLL – Small lymphocytic lymphoma.
[a] Asia Pacific: Australia; New Zealand; Korea; China; and Taiwan, China. *One patient without del17p was included in this cohort due to site error. This patient was not included in the efficacy analysis.
Source: SEQUOIA CSR[75]

B.2a.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence: previously untreated CLL

B.2a.4.1 Sample size calculations

Approximately 710 patients were to be enrolled in SEQUOIA, with 450 patients without 17p deletion in Cohort 1 available for the primary efficacy analysis and approximately 100 patients with 17p deletion in Cohort 2.[75]

The sample size of 450 patients for Cohort 1 (approximately 225 subjects per treatment arm) was calculated to detect a hazard ratio (HR) of 0.58 for IRC-assessed PFS at a power of approximately 84%. One final and one interim analysis were planned, with the final analysis planned when 118 IRC-assessed PFS events had been observed across arm A and arm B. The interim analysis was planned when approximately 73% of the required IRC-assessed PFS events for final analysis had occurred.[75]

The sample size selection for Cohorts 2 was driven by estimated patient availability.

B.2a.4.2 Statistical analysis

Table 15 summarises the statistical analyses used in Cohort 1 of SEQUOIA. All efficacy analyses were conducted based on the ITT population, which included all enrolled patients who were assigned to a treatment group. The safety analysis set included all patients who received any dose of study drug.

In Cohort 2, PFS, ORR and DOR were summarised descriptively by both IRC- and INV-assessment. The KM method was used to summarise the distribution of PFS and DOR including quartiles and event-free rates at selected timepoints. An estimate of ORR with 95% Clopper-Pearson confidence interval (CI) was generated.[75]

Table 15: Summary of prespecified statistical analyses used in SEQUOIA in Cohort 1

Endpoint	Analysis	Population
Primary endpoint analyses		
PFS (IRC)	• Log-rank test stratified by randomisation stratification factors (age [< 65 years versus ≥ 65 years], Binet stage [C versus A or B], and IGHV mutational status [mutated versus unmutated) • HR and 2-sided 95% CI estimated from a stratified Cox regression model • Distribution of PFS estimated using the Kaplan-Meier method	ITT population
Secondary efficacy endpoint analyses		
ORR	• Clopper-Pearson 95% CI • Odds ratio in ORR calculated along with 2-sided 95% CI using stratified Cochran-Mantel-Haenszel method • Best overall response was defined as the best response recorded from randomisation until data cut or start of new CLL/SLL anticancer treatment • Patients with no post-baseline response assessment (due to any reason) were considered as non-responses	ITT population
OS	• Log-rank test stratified by the randomisation stratification factors age (< 65 years versus ≥ 65 years), Binet stage (C versus A or B) • HR and 2-sided 95% CI estimated from a stratified Cox regression model • Distribution of OS estimated using the Kaplan-Meier method	ITT population
DOR	• DOR summarised using the Kaplan-Meier method	ITT population
PFS (INV)	• Assessed as per methods for PFS (IRC)	ITT population
Patient-reported outcomes		
EORTC QLQ-C30	• Comparison using MMRM model to account for missing data under the missing at random assumption • The dependent variable of this model was the QLQ-C30 QoL score • The model included treatment, time, as well as the 3 randomisation stratification factors as fixed effects • Random effects included patient random intercept on QLQ-C30 QoL score • Random effects assumed to follow a normal distribution	ITT population
Safety endpoints		

Endpoint	Analysis	Population
AEs, SAEs and TEAEs	• Graded by NCI-CTCAE v4.03 or based on the Grading Scale for Hematologic Toxicity in CLL Studies • Classified and coded using MedDRA • Descriptive statistics used to analyse all safety data by treatment group • Descriptive analyses by system organ class, preferred term, severity, and relationship to study drug	Safety population
Subgroup analyses of efficacy endpoints		
Subgroup analysis	Subgroups including: • Age (< 65 years versus ≥ 65 years) and (< 65 years versus 65 to 75 years versus ≥ 75 years) • Sex (male versus female) • Race (White versus Black versus Asian versus all others) • Geographic region (North America versus Europe versus Asian Pacific) • Cancer type (CLL versus SLL) • Binet stage (C versus A or B) • ECOG (0 versus ≥ 1) • Bulky disease (longest diameter < 5 cm versus ≥ 5 cm and < 10 cm versus ≥ 10 cm) • Elevated lactate dehydrogenase at baseline (No [≤ ULN] versus Yes [> ULN] per central laboratory) • Cytopenias at baseline (Yes versus No) • Chromosome 11q deletion (Yes versus No) • Del(13q) (Yes versus No) • Complex karyotype (< 3 versus ≥ 3 abnormalities) and (< 5 versus ≥ 5 abnormalities) • Trisomy 12 (Yes versus No) • TP53 mutation (Yes versus No) • Serum β2 – microglobulin (≤ 3.5 mg/L versus > 3.5 mg/L)	ITT population subgroups

AE – Adverse event; CI – Confidence interval; CTCAE – Common Terminology Criteria for Adverse Events; CLL – Chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer quality of life questionnaire ; IRC – Independent Review Committee; INV – Investigator; ITT – Intention-to-treat; MMRM – Mixed model repeated measures; OS – Overall survival; ORR – Overall response rate; PFS – Progression-free survival; QoL – Quality of life; SAE – Serious adverse event; SLL – Small lymphocytic lymphoma; TEAE – Treatment emergent adverse event.
Source: SEQUOIA CSR[75]

B.2a.4.3 Participant flow

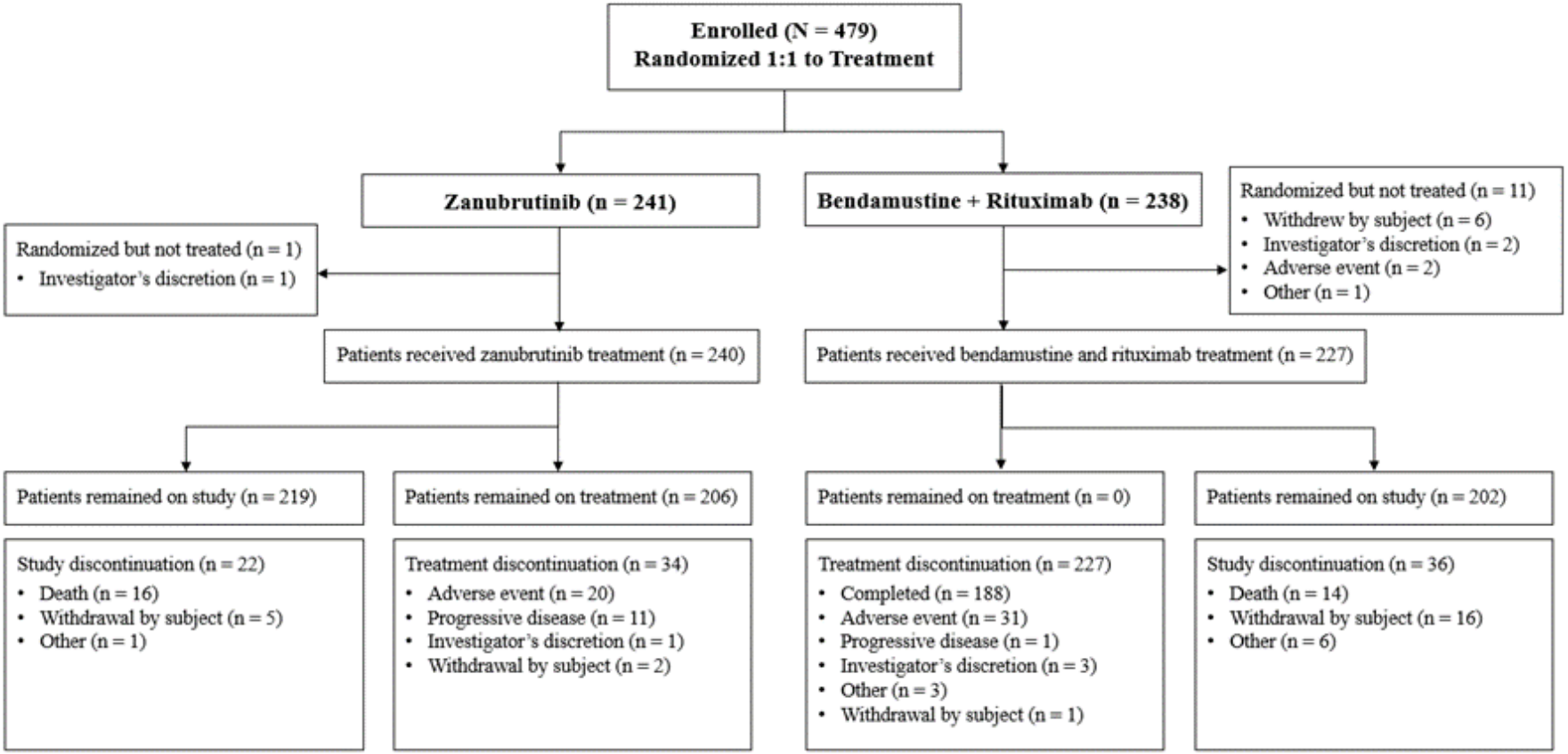
Cohort 1

As of the data cut-off date of 07 May 2021, 479 patients were randomised, of which 241 patients were allocated to the zanubrutinib arm and 238 patients were allocated to the BR arm. A total of 12 patients were randomised but did not receive any study treatment: one patient in the zanubrutinib arm, and 11 patients in the BR arm.[75]

The median follow-up for patients assigned to zanubrutinib and BR were 26.35 months and 25.92 months, respectively. In the zanubrutinib arm, 34 (14.1%) patients discontinued study treatment. The main reason for treatment discontinuation in the zanubrutinib arm was adverse events (AEs), reported in 20 (8.3%) patients. Given that BR was a fixed duration therapy, all 227 treated patients had discontinued therapy at the data cut-off date. In the BR arm, 188 (79.0%) patients had completed the prescribed duration of therapy and the most common reason for early treatment discontinuation was AEs with 31 (13.0%) patients discontinuing for this reason. In the BR arm, 15 (6.3%) patients initiated cross over to zanubrutinib monotherapy.[75]

The number of patients who discontinued treatment because of COVID-19-related AEs was five (2.1%) in the zanubrutinib arm. No dose modifications were observed in the BR arm due to COVID-19 since the pandemic began after all patients had concluded treatment with BR in Cohort 1. The number of patients who discontinued from the study because of fatal COVID-19-related AEs was five (2.1%) in the zanubrutinib arm and one (0.4%) in the BR arm.[75]

Figure 5: SEQUOIA: patient disposition in Cohort 1



Source: SEQUOIA CSR[75]

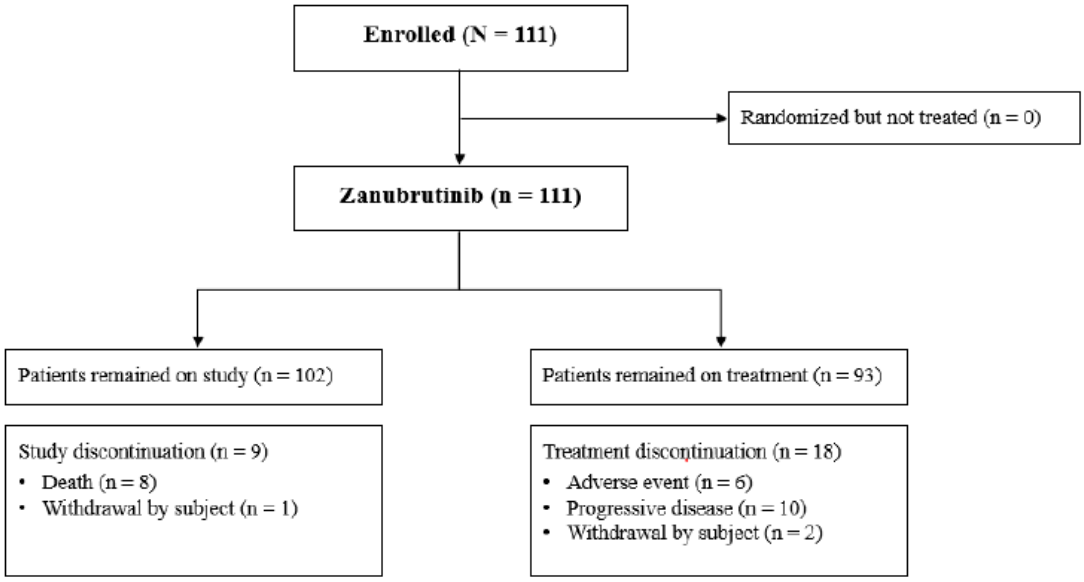
Cohort 2

As of the data cut-off date of 07 May 2021, 111 patients had been allocated to receive zanubrutinib in Cohort 2 and all patients received treatment.[75]

The median follow-up for zanubrutinib was 30.52 months and the majority of patients continued study treatment as of the data cut-off date, with only 18 (16.2%) patients discontinuing treatment. Of the patients discontinuing treatment, the most common reasons were disease progression and AE, which were reported in 10 (9.1%) and six (5.4%) patients, respectively.[75]

No patient in the zanubrutinib arm discontinued treatment because of COVID-19-related AE, though this caused dose interruption in three patients.[75]

Figure 6: SEQUOIA: patient disposition in Cohort 2



Source: SEQUOIA CSR[75]

B.2a.5 Critical appraisal of the relevant clinical effectiveness evidence: previously untreated CLL

A summary of the quality assessment for the SEQUOIA trial is provided in Table 16 for Cohort 1 and Table 17 for Cohort 2.

Table 16: Quality assessment results for SEQUOIA Cohort 1

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomised 1:1	Yes
Was the concealment of treatment allocation adequate?	Open-label study	No
Were the groups similar at the outset of the study in terms of prognostic factors	Baseline demographic and disease characteristics were similar between groups in terms of prognostic factors	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Patients and investigators were not masked to treatment. The IRC was blinded to study treatment.	No
Were there any unexpected imbalances in drop-outs between groups?	See section B.2a.4.3 Participant flow	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

CSR – Clinical study report; IRC – Independent review committee; NA – not applicable.

Table 17: Quality assessment results for SEQUOIA Cohort 2

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was the cohort recruited in an acceptable way?	Patients were recruited from 160 study locations and allocated to Cohort 2 dependent on mutation status	Yes
Was the exposure accurately measured to minimise bias?	See Section B.2a.10.1 Dose exposure	Yes

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was the outcome accurately measured to minimise bias?	See Section B.2a.3.3 Outcome measures	Yes
Have the authors identified all important confounding factors?	All important confounding factors were considered within pre-planned subgroup analyses. See Section B.2a.6 Clinical effectiveness results of the relevant studies	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Yes
Was the follow-up of patients complete?	See Section B.2a.6 Clinical effectiveness results of the relevant studies	Yes
How precise (for example, in terms of confidence interval and p values) are the results?	See Section B.2a.6 Clinical effectiveness results of the relevant studies	Yes

CSR – Clinical study report; IRC – Independent review committee; NA – not applicable.

B.2a.6 Clinical effectiveness results of the relevant studies: previously untreated CLL

The key efficacy outcomes for previously untreated patients with CLL from SEQUOIA are summarised in Table 18. Detailed results for Cohort 1 are presented in Section B.2a.6.1 Primary and key secondary endpoints: PFS in Cohort 1B.2a.6.3 Secondary endpoints in Cohort 1and detailed results for Cohort 2 are presented in Section B.2a.6.4 Secondary endpoints in Cohort 2.

Table 18: Key efficacy outcomes reported in SEQUOIA

	Cohort 1		Cohort 2
	Arm A: Zanubrutinib (N= 241)	**Arm B: BR (N= 238)**	**Arm C: Zanubrutinib (N= 110)**
IRC-assessed PFS (DCO 07 May 2021)			
Events, n (%)	36 (14.9)	71 (29.8)	15 (13.6)
HR (95% CI) [p-value]*	0.42 (0.28, 0.63); p<0.0001		-
INV-assessed PFS (DCO 07 May 2021)			
Events, n (%)	29 (12.0)	57 (23.9)	17 (15.5)
HR (95% CI) [p-value]*	0.42 (0.27, 0.66); p<0.0001		-
IRC-assessed ORR (DCO 07 May 2021)			
Complete response, n (%)	16 (6.6)	36 (15.1)	7 (6.4)
ORR, n (%) [95% CI]	228 (94.6) [91.0, 97.1]	203 (85.3) [80.1, 89.5]	99 (90.0) [82.8, 94.9]
Odds ratio (95% CI) [p-value]*	[redacted]		-
INV-assessed ORR (DCO 07 May 2021)			
Complete response, n (%)	22 (9.1)	44 (18.5)	10 (9.1)
ORR, n (%) [95% CI]	235 (97.5) [94.7, 99.1]	211 (88.7) [83.9, 92.4]	106 (96.4) [91.0, 99.0]
Odds ratio (95% CI) [p-value]*	[redacted]		-
OS (DCO 07 March 2022)			
Events, n (%)	[redacted]	[redacted]	[redacted]
IRC-assessed DOR (DCO 07 May 2021)			
Median, (95% CI)	NE (NE, NE)	30.6 (25.5, NE)	NE (NE, NE)
INV-assessed DOR (DCO 07 May 2021)			
Median, (95% CI)	NE (NE, NE)	30.6 (26.2, NE)	NE (NE, NE)

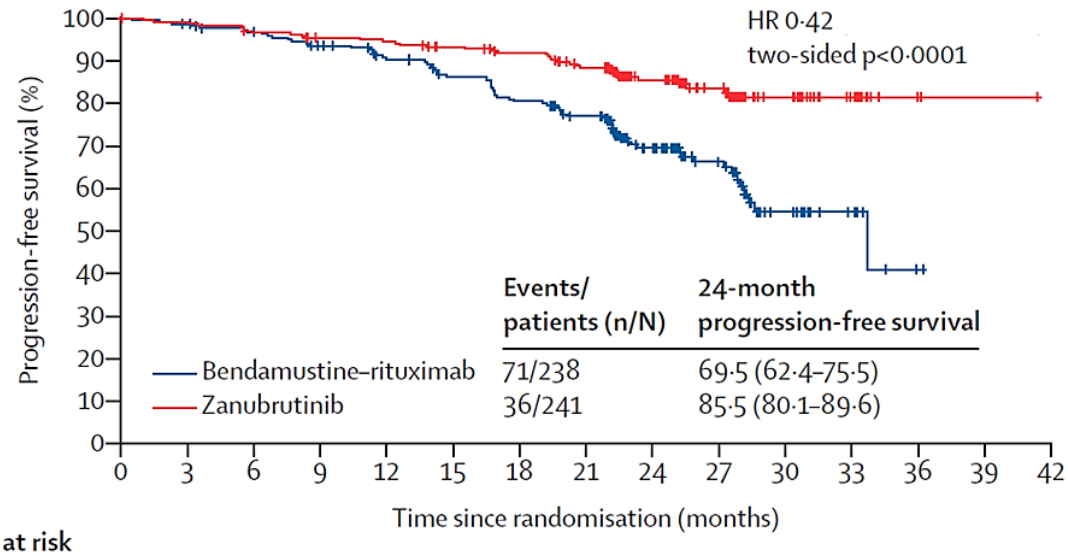
BR – Bendamustine-rituximab; CI – Confidence interval; DOR – Duration of response; INV – Investigator; IRC – Independent Review Committee; ORR - Overall response rate; OS – Overall survival; PFS – Progression-free survival.
*HR and 95% CI were from stratified Cox regression model with BR arm as the reference group.
Source: SEQUOIA CSR[75]

B.2a.6.1 Primary and key secondary endpoints: PFS in Cohort 1

The SEQUOIA trial met its primary endpoint, with zanubrutinib demonstrating a statistically significant improvement in IRC-assessed PFS compared to BR. When compared to treatment with BR, treatment with zanubrutinib was associated with a 58% reduction in the risk of disease progression or death (HR:0.42; 95% CI: 0.28, 0.63; p<0.0001).[75]

As shown in the KM plot presented in Figure 7, median PFS was not reached in the zanubrutinib arm, though was reached in the BR arm with a median of 33.7 months reported. As reported in Table 19, the event-free rates for patients in the zanubrutinib and BR arms, respectively, were reported as 94.5% and 90.2% at 12 months, 85.5% and 69.5% at 24 months, and 81.5% and 40.8% at 36 months. The median follow-up in the zanubrutinib and BR arms were 25.1 and 24.6 months, respectively.[75]

Figure 7: Kaplan–Meier plot for IRC-assessed PFS in SEQUOIA Cohort 1



Number at risk (number censored)															
Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	.. ..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)

BR – Bendamustine-rituximab; PFS – Progression-free survival; HR – hazard ratio; IRC – Independent review committee.
Source: Tam et al. (2022)[32]

In line with the IRC assessment of PFS, zanubrutinib demonstrated a statistically significant improvement in INV-assessed PFS compared to BR after a median follow-up of 22.8 and 22.6 months, respectively. When compared to treatment with BR, treatment with

zanubrutinib was associated with a 58% reduction in the risk of disease progression or death (HR:0.42; 95% CI: 0.27, 0.66; p<0.0001).[75]

As shown in the KM plot presented in Figure 9, median INV-assessed PFS was not reached in the zanubrutinib arm and was reported at 33.7 months in the BR arm. The event-free rates for patients in the zanubrutinib and BR arms, respectively, were reported as [redacted]% and [redacted]% at 12 months and [redacted]% and [redacted]% at 24 months. The concordance rate of PFS between the IRC- and INV-assessment was [redacted]%.[75]

Figure 8: Kaplan–Meier plot for INV-assessed PFS in SEQUOIA Cohort 1

BR – Bendamustine-rituximab; PFS – Progression-free survival; INV – investigator assessed.
Source: SEQUOIA CSR[75]

Table 19: IRC- and INV-assessed PFS in SEQUOIA Cohort 1

	Zanubrutinib (N = 241)	BR (N = 238)
IRC-assessed PFS, n (%)		
Events	36 (14.9)	71 (29.8)
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
HR (95% CI) [p-value]	0.42 (0.28, 0.63); p<0.0001	
Event-Free Rate at, % (95% CI) [a]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
Investigator-assessed PFS, n (%)		
Events	29 (12.0)	57 (23.9)
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
HR (95% CI) [p-value]*	0.42 (0.27, 0.66); p<0.0001	
Event-Free Rate at, % (95% CI) [a]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

BR – Bendamustine-rituximab; PFS – Progression-free survival; INV – investigator assessed; IRC – Independent review committee; NE – not estimable.
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
*HR and 95% CI were from stratified Cox regression model with BR arm as the reference group.
Source: SEQUOIA CSR[75]

B.2a.6.2 Sensitivity analysis of the primary endpoint – Cohort 1

As described in Table 20, exploratory sensitivity analyses, including PFS without stratification and without censoring, did not show significantly different results to the primary analysis, confirming the robustness of the primary analysis.

Table 20: Results of the sensitivity analysis for the primary endpoint (PFS by IRC)

Analysis	Zanubrutinib (N = 241)		BR (N = 238)		Hazard ratio	
	Events/ Patients (%)	Median (months) (95% CI)	Events/ Patients (%)	Median (months) (95% CI)	Hazard Ratio (95% CI)	P-value
Primary analysis	36/241 (14.9)	NE (NE, NE)	71/238 (29.8)	33.7 (28.1, NE)	0.42 (0.28, 0.63)	<.0001
Sensitivity analysis						
Unstratified analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on per-protocol analysis set	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiation of non-protocol CLL/SLL related therapy treated as PFS event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death or disease progression immediately after 2 or more missed consecutive disease assessment treated as a PFS event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BR – Bendamustine-rituximab; CLL – Chronic lymphocytic leukaemia; NE – not estimable; PFS – Progression-free survival; IRC – Independent review committee; SLL – Small lymphocytic lymphoma.
Source: SEQUOIA CSR[75]

B.2a.6.3 Secondary endpoints in Cohort 1

Overall response rate – Cohort 1

As demonstrated in Table 21, ORR determined by IRC-assessment was higher for patients in the zanubrutinib arm (94.6% [95% CI: 91.0%, 97.1%]) compared with the BR arm (85.3% [95% CI: 80.1%, 89.5%]), representing a statistically significant improvement in the odds of response [redacted][75]

Table 21: IRC- and INV-assessed response rates in SEQUOIA Cohort 1

	Zanubrutinib (N = 241)	BR (N = 238)
IRC-assessed response		
Best overall response, n (%)		
CR	16 (6.6)	36 (15.1)
nPR	3 (1.2)	14 (5.9)
PR	206 (85.5)	153 (64.3)
PRL	3 (1.2)	0 (0.0)
SD	7 (2.9)	14 (5.9)
PD	2 (0.8)	1 (0.4)
Not Evaluable	1 (0.4)	1 (0.4)
Discontinued Prior to First Assessment	3 (1.2)	19 (8.0)
Overall response rates		
ORR, n (%) [95% CI][a]	228 (94.6) [91.0, 97.1]	203 (85.3) [80.1, 89.5]
Odds ratio [95% CI]	[redacted]	
P-value	[redacted]	
INV-assessed response		
Best overall response, n (%)		
CR	22 (9.1)	43 (18.1)
CRi	0 (0.0)	1 (0.4)
nPR	5 (2.1)	18 (7.6)
PR	204 (84.6)	149 (62.6)
PRL	4 (1.7)	0 (0.0)
SD	3 (1.2)	5 (2.1)
PD	0 (0.0)	1 (0.4)

	Zanubrutinib (N = 241)	BR (N = 238)
Not Evaluable	0 (0.0)	1 (0.4)
Discontinued Prior to First Assessment	3 (1.2)	20 (8.4)
Overall response rates		
ORR, n (%) [95% CI][a]	235 (97.5) [94.7, 99.1]	211 (88.7) [83.9, 92.4]
Odds ratio [95% CI]	[redacted]	
P-value	[redacted]	

BR – Bendamustine-rituximab; CI – Confidence interval; CR – Complete response; IRC – Independent Review Committee; ORR – Overall response rate; PD – Progressive disease; PR – Partial response; PRL – Partial response with lymphocytosis; SD – Stable disease.
[a] Overall response is defined as achieving a best overall response of CR, CRi, nPR, PR, or PR-L.
Source: SEQUOIA CSR[75]

The ORRs determined by IRC-assessment were consistently observed across high-risk subgroups including age, Binet stage, baseline ECOG PS, bulky disease, IGHV mutational status, elevated LDH at baseline, cytopenias at baseline, 11q deletion, and serum β_2-microglobulin.[75]

Furthermore, the ORRs determined by IRC-assessment were consistent with those based on INV-assessment. In line with the ORR determined by IRC-assessment, the ORR determined by INV-assessment was higher for patients in the zanubrutinib arm (97.5% [95% CI: 94.7%, 99.1%]) compared with the BR arm (88.7% [95% CI: 83.9%, 92.4%]), representing a statistically significant improvement in the odds of response (OR: 5.22; 95% CI: 2.08, 13.08; p=0.0001). The complete response rate determined by INV-assessment was 9.1% and 18.5% in the zanubrutinib and BR arms, respectively.[75]

Overall survival – Cohort 1

As expected for long-term chronic illness such as CLL, OS data from SEQUOIA remains immature. As per the data-cut off on 07 March 2022, only [redacted] deaths had occurred in Cohort 1; [redacted] ([redacted]%) in the zanubrutinib arm and [redacted] ([redacted]%) in the BR arm after a median follow-up of 36.1 months and 35.4 months, respectively. When compared to treatment with BR, treatment with zanubrutinib was associated with a [redacted]% reduction in the risk of death [redacted][75]

As shown in the KM plot presented in Figure 9 and reported in Table 22, the event-free rates for patients in the zanubrutinib and BR arms, respectively, were reported as [redacted]% and [redacted]% at 12 months, [redacted]% and [redacted]% at 24 months, and [redacted]% and [redacted]% at 36 months.[75]

Figure 9: Kaplan–Meier plot for OS in SEQUOIA Cohort 1

BR – Bendamustine-rituximab; OS – Overall survival.
Source: SEQUOIA CSR[75]

Table 22: OS in SEQUOIA Cohort 1

	Zanubrutinib (N = 241)	BR (N = 238)
Deaths, n (%)	[redacted]	[redacted]
Event-Free Rate at, % (95% CI)		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

BR – Bendamustine-rituximab; CI – Confidence interval; OS – Overall survival.
Source: SEQUOIA CSR[75]

Duration of response – Cohort 1

As of the data cut-off of 07 May 2021 and at a median follow-up of 22.1 months in both arms, [redacted] ([redacted]%) patients on zanubrutinib and [redacted] ([redacted]%) patients on BR either had progressive disease (IRC-assessed) or had died. Median DOR was not reached in the zanubrutinib arm, though was reached in the BR arm with a median of 30.6 months reported. As reported in Table 23, the event-free rates for patients in the zanubrutinib and BR arms, respectively, were reported as [redacted]% and [redacted]% at 12 months, [redacted]% and [redacted]% at 24 months, and [redacted]% and NE at 36 months.[75]

DOR determined by INV-assessment was comparable to DOR determined by IRC-assessment, with [redacted] ([redacted]%) patients on zanubrutinib and [redacted] ([redacted]%) patients on BR having either progressive disease (INV-assessed) or had died at a median follow-up of 19.8 months across both arms.[75]

Table 23: IRC- and INV-assessed DOR in SEQUOIA Cohort 1

	Zanubrutinib (N = 241)	BR (N = 238)
IRC-assessed DOR, n (%)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Median DOR (months) (95% CI)	NE (NE, NE)	30.6 (25.5, NE)
Event free rate at, % (95% CI)[a]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
INV-assessed DOR, n (%)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Median DOR (months) (95% CI)	NE (NE, NE)	30.6 (26.2, NE)
Event free rate at, % (95% CI)[a]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

BR – Bendamustine-rituximab; CI – Confidence interval; DOR – Duration of response; INV – investigator assessed; IRC – independent review committee.
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: SEQUOIA CSR[75]

Patient-reported outcomes – Cohort 1

Patients in the zanubrutinib arm reported better overall outcomes than patients in the BR arm when using the EORTC QLQ-C30 instrument as indicated in the mean changes from baseline to Week 24 of the PRO key endpoints of global health status (GHS), physical and role functions scales and decreased symptoms of fatigue and nausea/vomiting and diarrhoea. The mean change from baseline in EORTC QLQ-C30 is described in Table 24.[75]

The least squares (LS) mean of change from baseline showed the zanubrutinib arm experienced significant improvements, as indicated by the LS mean difference at Week 24 in GHS ([redacted]), physical function ([redacted] role functioning ([redacted]), fatigue ([redacted]), nausea/vomiting [redacted]), and diarrhoea ([redacted]) compared with the BR arm. The LS difference between the two arms in pain was significant at Week 12 ([redacted]) but not at Week 24.[75]

Table 24: Mean change from baseline in EORTC QLQ-C30

PRO endpoint	Zanubrutinib, mean change from baseline (SD)		BR, mean change from baseline (SD)	
	Week 12	Week 24	Week 12	Week 24
GHS/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Physical function	[redacted]	[redacted]	[redacted]	[redacted]
Role function	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]

BR – Bendamustine-rituximab; GHS – Global health status; PRO – Patient reported outcome; QoL – Quality of life; SD – Standard deviation.
Source: SEQUOIA CSR[75]

A comparable improvement was observed in both the zanubrutinib and BR arms when using the EQ-5D-5L instrument (Mean [SD]) in the visual analogue scale (VAS) at Week 12 (Zanubrutinib: [redacted]; BR: [redacted]) and Week 24 (Zanubrutinib: [redacted]; BR: [redacted]), indicating that quality of life was maintained following treatment with zanubrutinib.[75]

B.2a.6.4 Secondary endpoints in Cohort 2

Overall response rate in Cohort 2 (IRC assessed)

As presented in Table 25, ORR determined by IRC-assessment was 90.0% (95% CI: 82.8, 94.9) with 88.2% (95 CI: 80.6, 93.6) having a best overall response of PR or higher. The ORRs determined by IRC-assessment were consistently observed across high-risk subgroups including age, Binet stage, baseline ECOG PS, bulky disease, IGHV mutational status, elevated LDH at baseline, cytopenias at baseline, 11q or 13q deletion, Trisomy 12, TP53 mutation, and serum β2-microglobulin.[75]

Table 25: IRC-assessed response rates in SEQUOIA Cohort 2

	Zanubrutinib (N = 110)
IRC-assessed response	
Best overall response, n (%)	
CR	7 (6.4)
nPR	2 (1.8)
PR	88 (80.0)
PRL	2 (1.8)
SD	11 (10.0)
Overall response rates[a]	
ORR, n (%) [95% CI]	99 (90.0) [82.8, 94.9]
INV-assessed response	
Best overall response, n (%)	
CR	10 (9.1)
nPR	4 (3.6)
PR	91 (82.7)
PRL	1 (0.9)
SD	3 (2.7)
PD	1 (0.9)
Overall response rates[a]	
ORR, n (%) [95% CI]	106 (96.4) [91.0, 99.0]

CI – Confidence interval; CR – Complete response; IRC – Independent Review Committee; ORR – Overall response rate; PR – Partial response; PRL – Partial response with lymphocytosis.
[a] Overall response is defined as achieving a best overall response of CR, CRi, nPR, PR, or PR-L.
Source: SEQUOIA CSR[75]

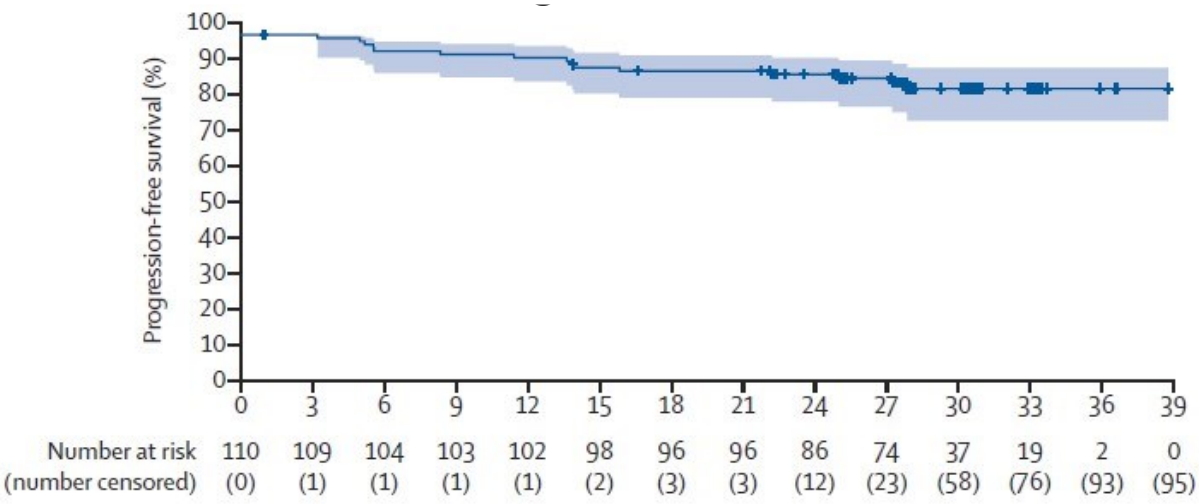
Furthermore, the ORRs determined by IRC-assessment were consistent with those based on INV-assessment. In line with the ORR determined by IRC-assessment, the ORR

determined by INV-assessment was 96.4% (95% CI: 91.0, 99.0) with 95.5% (95% CI: 89.7; 98.5) having a best overall response of PR or higher. In addition, the ORRs determined by both IRC- and INV-assessment were comparable for zanubrutinib across Cohort 1 and Cohort 2 demonstrating that depth of response following treatment with zanubrutinib is consistent across both the 'unfit' and 'high-risk' populations.[75]

PFS in Cohort 2

As of data cut-off of 07 May 2021 and median follow-up of 27.9 months, median IRC-assessed PFS was not reached in Cohort 2. As shown in the KM plot presented in Figure 10 and reported in Table 26, the event-free rates at 12, 24, and 36 months were 93.6%, 88.9%, and 84.9%, respectively.[75]

Figure 10: Kaplan–Meier plot for IRC-assessed PFS in SEQUOIA Cohort 2



PFS – Progression-free survival; IRC – Independent review committee.
Source: Tam et al. (2022)[32]

PFS appeared to be preserved across high-risk subgroups including age, Binet stage, ECOG status, bulky disease, IGHV mutational status and baseline cytopenias. Patients with concurrent TP53 mutation had a numerically higher rate of progression.[75]

In line with the IRC assessment of PFS, median INV-assessed PFS was not reached in Cohort 2 at a median follow-up of 27.7 months. Overall, the event-free rates at 12, 24, and 36 months were [redacted]%, [redacted]%, and [redacted]%, respectively. In addition, PFS determined by both IRC and INV assessment were comparable for zanubrutinib across Cohort 1 and Cohort 2 demonstrating that the treatment effect is consistent across both the 'unfit' and 'high-risk' populations.[75]

Table 26: IRC- and INV-assessed PFS in SEQUOIA Cohort 2

	Zanubrutinib (N = 110)
IRC-assessed PFS events, n (%)	
Events	[redacted]
Progressive disease	[redacted]
Death	[redacted]
IRC-assessed Event-Free Rate at, % (95% CI)[a]	
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
36 months	[redacted]
INV-assessed PFS events, n (%)	
Events	[redacted]
Progressive disease	[redacted]
Death	[redacted]
INV-assessed Event-Free Rate at, % (95% CI)[a]	
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
36 months	[redacted]

PFS – Progression-free survival; IRC – Independent review committee; INV – investigator.
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: SEQUOIA CSR[75]

Duration of response in Cohort 2 (IRC assessed)

As of the data cut-off of 07 May 2021 and at a median follow-up of 25.1 months, [redacted] patients had progressive disease and no deaths were reported. As reported in Table 27, the event-free rates were [redacted]% and [redacted]% at 12 and 24 months, respectively.[75]

Table 27: DOR in SEQUOIA Cohort 2

	Zanubrutinib (N = 110)
IRC-assessed DOR, n (%)	
Events, n (%)	[redacted]
Progressive disease	[redacted]
Death	[redacted]
Median DOR (months) (95% CI)	[redacted]
Event free rate at, % (95% CI) [a]	
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
36 months	[redacted]
INV-assessed DOR, n (%)	
Events, n (%)	[redacted]
Progressive disease	[redacted]
Death	[redacted]
Median DOR (months) (95% CI)	[redacted]
Event free rate at, % (95% CI) [a]	
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
36 months	[redacted]

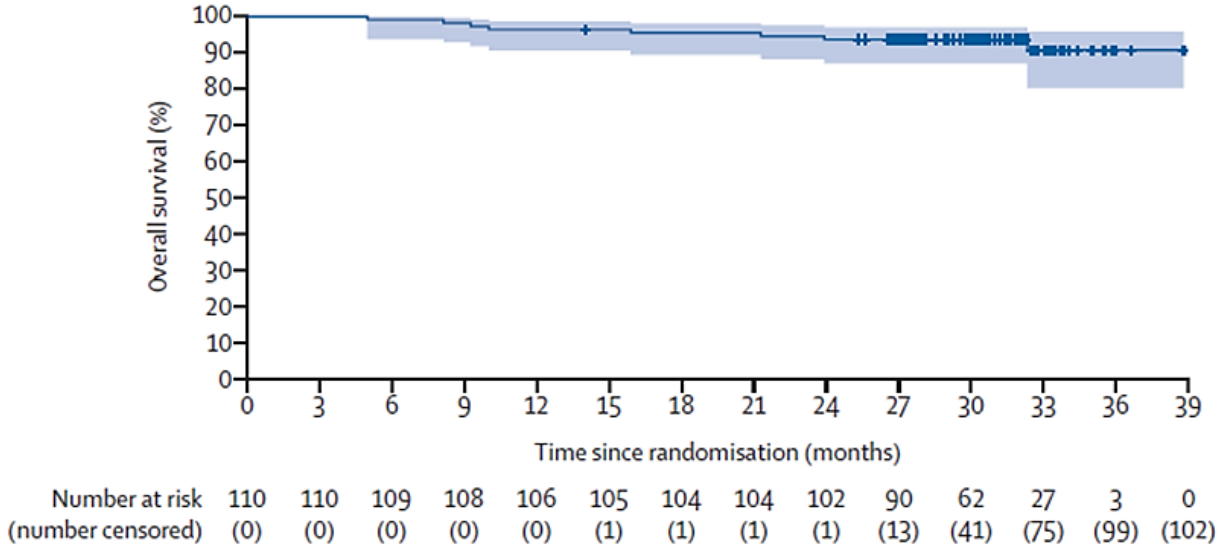
CI – Confidence interval; DOR – Duration of response; NE – not estimable.
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: SEQUOIA CSR[75]

DOR determined by INV-assessment was comparable to DOR determined by IRC-assessment, with [redacted] patients on zanubrutinib having either progressive disease or had died at a median follow-up of 24.9 months. In addition, DOR determined by both IRC- and INV-assessment were comparable for zanubrutinib across Cohort 1 and Cohort 2 demonstrating that the duration of response is consistent following treatment with zanubrutinib across both the 'unfit' and 'high-risk' populations.[75]

Overall survival in Cohort 2

As per the data-cut off on 07 May 2021, only [redacted] deaths were reported in Cohort 2 at a median follow-up time of 30.4 months. As presented in Table 28, the event-free rates were [redacted]%, [redacted]%, and [redacted]% at 12, 24, and 36 months, respectively and median OS was not reached. In addition, OS was comparable for zanubrutinib across Cohort 1 and Cohort 2 demonstrating that outcomes are consistent following treatment with zanubrutinib across both the 'unfit' and 'high-risk' populations.[75]

Figure 11: Kaplan–Meier plot for OS in SEQUOIA Cohort



CI – Confidence interval; OS – Overall survival.
Source: Tam et al. (2022)[32]

Table 28: OS in SEQUOIA Cohort 2

	Zanubrutinib (N = 110)
Events, n (%)	[redacted]
Event-Free Rate at, % (95% CI)	
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
36 months	[redacted]

CI – Confidence interval; OS – Overall survival.
Source: SEQUOIA CSR[75]

B.2a.7 Subgroup analysis: previously untreated CLL

As presented in Figure 12, for the primary endpoint of IRC-assessed PFS was consistently longer with zanubrutinib than BR across key prespecified subgroups in Cohort 1, including:

- **Patients with 11q deletion** showed a statistically significant PFS benefit with zanubrutinib compared to BR (HR: 0.21; 95% CI: 0.09, 0.50).
- **Patients with serum β_2 microglobulin greater than 3.5mg/L** showed a statistically significant PFS benefit with zanubrutinib compared to BR (HR: 0.58; 95% CI: 0.36, 0.95).
- **Patients with IGHV unmutated** showed a statistically significant PFS benefit with zanubrutinib compared to BR (HR: 0.24; 95% CI: 0.13, 0.43).
- **Patients with bulky disease 5 cm or greater** showed a statistically significant PFS benefit with zanubrutinib compared to BR (HR: 0.52; 95% CI: 0.27, 0.97).[75]

Figure 12: Forest plot of hazard ratio of PFS by IRC in SEQUOIA Cohort 1

BR – Bendamustine-rituximab; CLL – Chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; IgVH – Immunoglobulin heavy chain gene; PFS – Progression-free survival; IRC – Independent review committee; LDi – Longest diameter; SLL – Small lymphocytic lymphoma; TP53 – Tumour protein P55.
[a] HR and 95% CI were from stratified (for all patients) or unstratified (for subgroup) analysis Cox regression model with BR arm as the reference group.
[b] Cytopenia: patients having anaemia or thrombocytopenia or neutropenia.
[c] Based on monosomy 13q mutation results. *Source: SEQUOIA CSR*[75]

B.2b.3 Summary of methodology of the relevant clinical effectiveness evidence: R/R CLL

B.2b.3.1 Study design

ALPINE is an international, randomised, open-label, multi-centre, phase 3 trial of zanubrutinib versus ibrutinib in patients with R/R CLL. The primary trial endpoint was INV-assessed ORR.[76]

A total of 652 patients were randomised 1:1 between zanubrutinib and ibrutinib, with randomisation stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/TP53 mutation status (present or absent). For the purposes of stratification, refractory disease was defined as either no objective response or disease progression within 6 months of the last CLL/SLL treatment, and relapsed disease was defined as disease that relapsed more than 6 months after the last CLL/SLL treatment was subsequently progressed.[76]

Table 29 summarises the ALPINE trial methodology and study design and randomisation is presented in Figure 13.

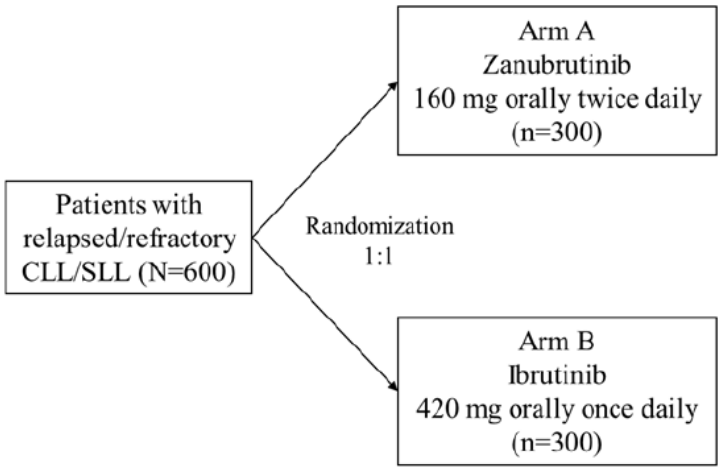
Table 29: Summary of trial methodology

Study details	ALPINE (BGB-3111-305; NCT03734016)
Location	Australia, Belgium, China, Czechia, France, Germany, Italy, Netherlands, New Zealand, Poland, Spain, Sweden, Turkey, United Kingdom
Design	Phase 3, open-label, randomised, multi-centre study in participants with relapsed/refractory CLL/SLL.
Randomisation	IRT was used to randomise patients 1:1 to either zanubrutinib or ibrutinib. Randomisation was stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/TP53 mutation status (present or absent)
Blinding	This was an open-label study; however, the IRC for response assessment was blinded to study treatment. Whilst the independent DMC was not blinded due to the open-label nature of the study, the sponsor did not have access to aggregated data summaries by actual study treatment assignment while the study was ongoing to avoid unwanted bias.
Treatment	**Arm A (zanubrutinib):** • Oral zanubrutinib 160 mg twice a day (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression. **Arm B (ibrutinib):** • Oral ibrutinib 420 mg once a day (three 140 mg capsules once a day) until unacceptable toxicity or disease progression.

Endpoints	**Primary endpoint:** • ORR (INV) **Secondary endpoint:** • PFS (IRC and INV*) • Safety parameters* • DOR (IRC and INV) • TTTF • OS • PROs (EORTC QLQ-C30, EQ-5D-5L)
Subgroup analysis	Sex, age, geographic region, race, ECOG performance status, patients with positive HBcAb, time from initial diagnosis to randomisation, disease type (CLL/SLL), disease stage, bulky disease, del 17p status, del 11q status, TP53 mutation status, beta 2 microglobulin, IGVH mutation status and complex karyotype.

CLL – Chronic lymphocytic leukaemia; DMC – Data Monitoring Committee; DOR – Duration of response; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D – 5-dimension EuroQol questionnaire; IRC Investigator Review Committee; INV – Investigator; IRT – Interactive Response Technology; IGHV – Immunoglobulin heavy chain gene; LDH – Lactate dehydrogenase; PFS – Progression-free survival; PRO – Patient reported outcome; ORR – Overall response rate; OS – Overall survival; SLL – Small lymphocytic lymphoma; TTTF – Time to treatment failure.
*INV-assessed PFS and the incidence of treatment-emergent atrial fibrillation/flutter were reported as key secondary outcomes of interest.
Source: ALPINE CSR[76]

Figure 13: ALPINE study schematic



CLL – Chronic lymphocytic leukemia; SLL – Small lymphocytic lymphoma.
Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/*TP53* mutation status (present versus absent).
Source: ALPINE CSR[76]

B.2b.3.2 Eligibility criteria

Eligible patients were aged ≥18 years with a diagnosis of CLL/SLL meeting the iwCLL criteria who were R/R to at least one prior systemic therapy for CLL/SLL. Key inclusion and exclusion criteria for the ALPINE trial are presented in Table 30.

Table 30: Key eligibility criteria for ALPINE

Key inclusion criteria
• Age 18 years or older • Confirmed diagnosis of CLL or SLL that met the iwCLL criteria[27] and requiring treatment as defined by specific criteria • R/R to at least one prior systemic therapy for CLL/SLL • Measurable disease by CT/MRI, with measurable disease defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters or an extranodal lesion > 10 mm in longest perpendicular diameter • ECOG performance status of 0, 1 or 2 • Life expectancy 6 months or higher • Adequate bone marrow and organ function by specific criteria • Adequate renal and hepatic function
Key exclusion criteria
• Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation • Clinically significant cardiovascular disease • Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast • History of severe bleeding disorder, or history of spontaneous bleeding requiring blood transfusion or other medical intervention • History of stroke or intracranial haemorrhage within 180 days before first dose of study drug • Severe or debilitating pulmonary disease • Active fungal, bacterial, and/or viral infection requiring systemic therapy • Known central nervous system involvement by leukaemia or lymphoma • Prior treatment with BTKi • Vaccination with a live vaccine within 35 days prior to the first dose of study drug

CLL – chronic lymphocytic leukaemia; BTKi – Bruton tyrosine kinase inhibitor; CT – computerised tomography; ECOG – European Cooperative Oncology Group; iwCLL – International Workshop on Chronic Lymphocytic Leukemia; MRI – magnetic resonance imaging; R/R – relapsed/refractory; SLL – Small lymphocytic lymphoma.
Source: ALPINE CSR[76]

B.2b.3.3 Outcome measures

The definition of the outcome measures available in the ALPINE study are presented in Table 31.

Table 31: Outcome measures available from ALPINE

Efficacy measures	Description	Datacut available[a]	Used in economic model
Primary			
ORR (INV)	The proportion of patients achieving a best overall response of CR, CRi, nPR or PR determined by INV assessment using the iwCLL guidelines[27] with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL)	01 December 2021	No
Secondary			
PFS (INV and IRC)	Time from randomisation to the date of first documentation of disease progression or death, whichever occurred first, as determined by INV or IRC assessment	01 December 2021	Yes
		08 August 2022 [b]	No
DOR (INV and IRC)	Time from the date that response criteria were first met to the date that disease progression was objectively documented or death, whichever occurs first, as determined by INV or IRC assessment	01 December 2021	No
TTTF	Time from randomisation to discontinuation of study drug due to any reason	01 December 2021	No
OS	Time from randomisation to the date of death due to any cause	01 December 2021	Yes
HRQoL (EORTC QLQ-C30, EQ-5D-5L)	Change from baseline in EORTC QLQ-C30 and EQ-5D-5L scores	01 December 2021	Yes
Safety	AEs classified based on MedDRA (Version 20.0 or higher) and graded according to the NCI-CTCAE (version 4.03)	01 December 2021	Yes

AE – Adverse events; CR – Complete response; CRi – Complete response with incomplete bone marrow recovery; CTCAE – Common Terminology Criteria for Adverse Events; DOR – Duration Of Response; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer Core Quality of Life; EQ-5D – EuroQol 5-Dimensions; HRQoL – Health-Related Quality of Life; INV – Investigator; IRC – Independent Review Committee; iwCLL – International Workshop on Chronic Lymphocytic Leukaemia; nPR – nodular partial remission; NHL – Non Hodgkin's Lymphoma; ORR – Overall Response Rate; OS – Overall Survival; PFS – Progression free survival; PR – Partial response; SD – Stable disease; SLL – Small lymphocytic lymphoma; TTTF – Time to treatment failure.

[a]Median follow-up for 01 December 2021 data-cut: 24.34 months in the zanubrutinib arm and 23.82 months in the ibrutinib arm. Median follow-up for 08 August 2022 data-cut: 32.00 months in the zanubrutinib arm and 27.89 months in the ibrutinib arm.

[b]2022 data cut became available following the preparation of the economic models and is not expected to impact the cost-effectiveness estimates.

Source: ALPINE CSR[76]

B.2b.3.4 Patient characteristics

Demographic and baseline characteristics were generally balanced between the zanubrutinib arm and ibrutinib arm in the ITT Analysis Set as presented in Table 32.

However, small differences were seen in sex and age. The zanubrutinib arm had a higher proportion of female patients (34.9%) compared with the ibrutinib arm (28.6%). The median age was 67 years in the zanubrutinib arm and 68 years in the ibrutinib arm, though the proportion of patients of ≥ 75 years in the zanubrutinib arm (22.6%) was comparable to that in the ibrutinib arm (21.2%). The majority of patients were white (79.8% in the zanubrutinib arm; 83.1% in the ibrutinib arm) and randomised at sites in Europe, including 32 patients from UK sites. In addition, almost all patients across both arms had an ECOG PS of 0 or 1 (97.9% in the zanubrutinib arm; 96% in the ibrutinib arm).[76]

Table 32: Baseline patient and disease characteristics in ALPINE

	Zanubrutinib (N=327)	**Ibrutinib (N=325)**
Cancer type, n (%)		
CLL	314 (96.0)	309 (95.1)
SLL	13 (4.0)	16 (4.9)
Age, (years)		
Mean (SD)	66.7 (10.18)	67.1 (9.18)
Median	67.0	68.0
<65 years	126 (38.5)	125 (38.5)
≥65 and < 75 years	127 (38.8)	131 (40.3)
≥75 years	74 (22.6)	69 (21.2)
Sex, n (%)		
Male	213 (65.1)	232 (71.4)
Female	114 (34.9)	93 (28.6)
Race, n (%)[a]		
Asian	47 (14.4)	44 (13.5)
White	261 (79.8)	270 (83.1)
Other	10 (3.1)	4 (1.2)
Unknown	9 (2.8)	7 (2.2)
Geographic region, n (%)		
Asia	49 (15.0)	45 (13.8)
Australia/New Zealand	28 (8.6)	30 (9.2)
Europe	198 (60.6)	191 (58.8)
North America	52 (15.8)	59 (18.2)

	Zanubrutinib (N=327)	Ibrutinib (N=325)
ECOG performance status, n (%)		
0-1	320 (97.9)	312 (96.0)
2	7 (2.1)	13 (4.0)
Time from initial diagnosis of CLL/SLL to randomisation, months		
Mean (SD)	90.0 (55.07)	94.1 (60.43)
Median	83.5	82.0
Binet stage at study entry for CLL, n (%)		
A/B	182 (55.7)	189 (58.2)
C	145 (44.3)	135 (41.5)
Missing	0 (0.0)	1 (0.3)
Del17p, n (%)		
Yes	45 (13.8)	50 (15.4)
No	282 (86.2)	275 (84.6)
TP53 mutation, n (%)		
Yes	50 (15.3)	45 (13.8)
No	276 (84.4)	280 (86.2)
Missing	1 (0.3)	0 (0.0)
Del 17p and/or TP53 mutation status, n (%)		
Yes	75 (22.9)	75 (23.1)
No	251 (76.8)	250 (76.9)
Missing	1 (0.3)	0 (0.0)
IGVH mutation status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Missing	9 (2.8)	16 (4.9)
β_2 microglobulin, n (%)		
≤ 3.5 mg/L	104 (31.8)	92 (28.3)
> 3.5 mg/L	177 (54.1)	183 (56.3)
Missing	46 (14.1)	50 (15.4)

CLL – Chronic lymphocytic leukemia; ECOG – Eastern Cooperative Oncology Group; SD – Standard deviation; SD – Standard deviation; SLL – Small lymphocytic lymphoma.
[a]Unknown= Unknown or not reported. Other = Other, multiple, black or African American, or Native Hawaiian or Other Pacific Islander.
Source: ALPINE CSR[76]

B.2b.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence: R/R CLL

B.2b.4.1 Sample size calculations

The sample size of 600 (approximately 300 patients per treatment arm) was calculated to detect a response ratio of 1.03 for INV-assessed ORR at a power greater than 90% to demonstrate non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 0.8558 (response ratio). Superiority testing with a 1-sided significance level of 0.005 at the interim analysis and 0.0235 at the final analysis of overall response rate correspond to a chi-squared p-value cut-off of 0.0099 and 0.0469, respectively.[76]

One final and one interim analysis were planned, with the final analysis planned when 205 events were observed, which was estimated to occur approximately 45 months after study start. The interim analysis was planned at 69% information fraction once approximately 415 patients had been randomised.[76]

B.2b.4.2 Statistical analysis

Table 33 summarises the statistical analyses used in ALPINE. All efficacy analyses were conducted based on the ITT population, which included all enrolled patients who were assigned to a treatment group. The safety analysis set included all patients who received any dose of study drug.

Table 33: Summary of prespecified statistical analyses used in ALPINE

Endpoint	Analysis	Population
Primary endpoint analyses		
ORR	• Clopper-Pearson 95% CIs • Response ratio in ORR calculated along with 2-sided 95% CI using stratified Cochran-Mantel-Haenszel method • Response ratio is estimated as ORR of zanubrutinib divided by that of ibrutinib • Best overall response defined as the best response from the randomisation date to the data cut-off date, disease progression, or the start of new CLL/SLL therapy • ORR defined as PR or higher (CR/CRi + PR + nodular PR) • Responders defined as patients with a best overall response of PR or higher	ITT population
Secondary efficacy endpoint analyses		
PFS	• Log-rank test stratified by randomisation factors (age [< 65 years versus ≥ 65 years], geographic region [China versus non-China], refractory status [yes or no], and del(17p)/TP53 mutation status [present or absent]) • HR and 2-sided 95% CI estimated from a stratified Cox regression model • Distribution of PFS estimated using the Kaplan-Meier method	ITT population
OS	• Log-rank test stratified by randomisation factors (age [< 65 years versus ≥ 65 years], geographic region [China versus non-China], refractory status [yes or no], and del(17p)/TP53 mutation status [present or absent]) • HR and 2-sided 95% CI estimated from a stratified Cox regression model • Distribution of PFS estimated using the Kaplan-Meier method	ITT population
DOR	• DOR summarised using the Kaplan-Meier method	ITT population
TTF	• Treatment failure defined as the discontinuation of study treatment for any reason. • Cox regression model stratified by randomisation factors (age [< 65 years versus ≥ 65 years], geographic region [China versus non-China], refractory status [yes or no], and del(17p)/TP53 mutation status [present or absent])	ITT population
Patient-reported outcomes		
EORTC QLQ-C30	• Comparison using MMRM model to account for missing data under the missing at random assumption • MMRM performed in key endpoints, including GHS/QoL, physical functioning, role functioning, fatigue, nausea/vomiting, diarrhoea, and pain • The dependent variable of this model was the QLQ-C30 QoL score, and the model included treatment and time	ITT population
Safety endpoints		

Endpoint	Analysis	Population
AEs, SAEs and TEAEs	• Graded by NCI-CTCAE v4.03 or based on the Grading Scale for Hematologic Toxicity in CLL Studies • Classified and coded using MedDRA • Descriptive statistics used to analyse all safety data by treatment group • Descriptive analyses by system organ class, preferred term, severity, and relationship to study drug	Safety population
Subgroup analyses of efficacy endpoints		
Subgroup analyses	Subgroups including: • Age (< 65 years versus ≥ 65 years) • Sex (male versus female) • Race (White versus Asian versus all others) • Geographic region (China versus non China) • Cancer type (CLL versus SLL) • Binet stage (C versus A or B) • ECOG (0 versus ≥ 1) • Bulky disease (longest diameter < 5 cm versus ≥ 5 cm and < 10 cm versus ≥ 10 cm) • Chromosome 11q deletion (Yes versus No) • Del(13q) (Yes versus No) • Complex karyotype (< 3 versus ≥ 3 abnormalities) and (< 5 versus ≥ 5 abnormalities) • Del(17p)/TP53 mutation (Present versus Absent) • Serum β2 – microglobulin (≤ 3.5 mg/L versus > 3.5 mg/L)	ITT population

AE – Adverse event; CI – Confidence interval; CTCAE – Common Terminology Criteria for Adverse Events; CLL – Chronic lymphocytic leukaemia; CR – complete response; CRi – Complete remission with incomplete haematological recovery; ECOG – Eastern Cooperative Oncology Group; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer quality of life questionnaire ; HR – hazard ratio; IRC – Independent Review Committee; ITT – Intention-to-treat; MMRM – Mixed model repeated measures; OS – Overall survival; ORR – Overall response rate; PFS – Progression-free survival; PR – partial response; QoL – Quality of life; SAE – Serious adverse event; SLL – Small lymphocytic lymphoma; TEAE – Treatment-emergent adverse event.
Source: ALPINE CSR[76]

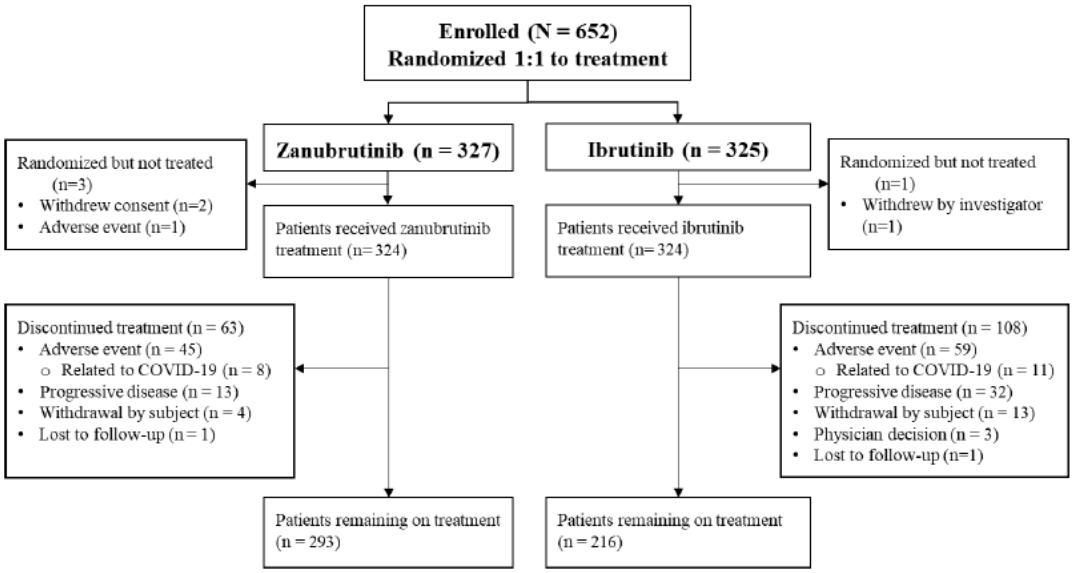
B.2b.4.3 Participant flow

As of the data cut-off date of 01 December 2021, 652 patients were randomised, of which 327 patients were allocated to the zanubrutinib arm and 325 patients were allocated to the ibrutinib arm. A total of four patients were randomised but did not receive treatment: three in the zanubrutinib arm and one in the ibrutinib arm.[76]

The median follow-up for patients assigned to zanubrutinib and ibrutinib were 24.34 and 23.82 months, respectively. In the zanubrutinib arm, 63 (19.3%) patients discontinued study treatment, with 45 (13.8%) patients discontinuing due to AEs and 13 (4%) patients discontinuing due to progressive disease. In comparison, 108 (33.2%) patients discontinued treatment in the ibrutinib arm, with 59 (18.2%) patients discontinuing due to AEs and 32 (9.8%) patients discontinuing due to progressive disease.[76]

The number of patients who discontinued treatment because of COVID-19-related AEs were eight (2.4%) in the zanubrutinib arm and 11 (3.4%) in the ibrutinib arm. All of the COVID-19-related AEs led to fatality.[76]

Figure 14: Patient disposition (ITT analysis set)



ITT – Intent to treat.
Source: ALPINE CSR[76]

B.2b.5 Critical appraisal of the relevant clinical effectiveness evidence: R/R CLL

A summary of the quality assessment for the ALPINE trial is provided in Table 34.

Table 34: Quality assessment results for ALPINE

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomised 1:1	Yes
Was the concealment of treatment allocation adequate?	Open-label study	No
Were the groups similar at the outset of the study in terms of prognostic factors	Baseline demographic and disease characteristics were similar between groups in terms of prognostic factors	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Patients and investigators were not masked to treatment. The IRC was blinded to study treatment.	No
Were there any unexpected imbalances in drop-outs between groups?	See section B.2b.4.3 Participant flow	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

CSR – clinical study report; IRC – independent review committee; NA – not applicable.

B.2b.6 Clinical effectiveness results of the relevant studies: R/R CLL

The key efficacy outcomes for patients with R/R CLL from ALPINE are summarised in Table 35 with all data in the clinical and economic sections based on the interim data cut conducted on 01 December 2021. Late breaking PFS data, with a data cut-off 08 August 2022 is presented within the clinical evidence only.[77] This data only became available following the preparation of the economic models and is not expected to impact the cost-effectiveness estimates.

Table 35: Key efficacy outcomes reported in ALPINE

	Zanubrutinib (N=327)	Ibrutinib (N=325)
INV-assessed ORR (DCO 01 December 2021)		
Complete response, n (%)	[redacted]	[redacted]
Overall response rate, n (%) [95% CI]	[redacted]	[redacted]

Response ratio[b] (95% CI) [p-value]	[redacted]	
IRC-assessed ORR (DCO 01 December 2021)		
Complete response, n (%)	[redacted]	[redacted]
Overall response rate, n (%) [95% CI]	[redacted]	[redacted]
Response ratio[b] (95% CI) [p-value]	[redacted]	
INV-assessed PFS (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]	
INV-assessed PFS (DCO 08 August 2022)		
Events, n (%)	87 (26.6)	118 (36.3)
HR (95% CI) [p-value]	0.65 (0.49, 0.86); p=0.0024[a]	
Median (95% CI) [months]	NE (34.3, NE)	34.2 (33.3, NE)
IRC-assessed PFS (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]	
IRC-assessed PFS (DCO 08 August 2022)		
Events, n (%)	88 (26.9)	120 (36.9)
HR (95% CI) [p-value]	0.65 (0.49, 0.86); p=0.0024[a]	
INV-assessed DOR (DCO 01 December 2021)		
Median, (95% CI)	[redacted]	[redacted]
IRC-assessed DOR (DCO 01 December 2021)		
Median, (95% CI)	[redacted]	[redacted]
TTTF (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
OS (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]

CI – Confidence interval; DCO – Data cut-off; DOR – Duration of response; HR – Hazard ratio; INV – Investigator; IRC – Independent Review Committee; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; TTTF – Time to Treatment Failure.
[a] Superiority 2-sided p-value.
[b] Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.
Source: ALPINE CSR[76], Brown et al.[77]

B.2b.6.1 Primary and key secondary endpoints: ORR

The ALPINE trial met its primary endpoint, with zanubrutinib demonstrating a statistically significant improvement in ORR determined by INV-assessment. As demonstrated in Table 36, ORR determined by INV-assessment was higher for patients in the zanubrutinib arm [redacted] compared with the ibrutinib arm [redacted], representing a response ratio of [redacted]

[redacted]. The complete response rate determined by INV-assessment was higher in the zanubrutinib arm [redacted] than the ibrutinib arm [redacted][76]

In line with the ORR determined by INV-assessment, the ORR determined by IRC-assessment was higher for patients in the zanubrutinib arm [redacted] compared with the ibrutinib arm [redacted], representing a response ratio of [redacted] The complete response rate determined by INV-assessment was higher in the zanubrutinib arm [redacted] than the ibrutinib arm [redacted][76] Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, demonstrated that the difference in ORR between zanubrutinib and ibrutinib further increased (83.5% for zanubrutinib and 74.2% for ibrutinib), further highlighting the improved outcomes on zanubrutinib.[77]

The concordance rates for best overall response of PR or higher between IRC and INV assessments were [redacted] and [redacted] for the zanubrutinib and ibrutinib arms, respectively (Table 14.2.1.2).[76]

Table 36: INV- and IRC-assessed response rates in ALPINE

	Zanubrutinib (N = 327)	**Ibrutinib (N = 325)**
INV-assessed response		
Best overall response, n (%)		
CR	[redacted]	[redacted]
Cri	[redacted]	[redacted]
NPR	[redacted]	[redacted]
PR	[redacted]	[redacted]
PRL	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Discontinued prior to first assessment	[redacted]	[redacted]
Not assessed	[redacted]	[redacted]
Overall response rates		
ORR, n (%)[a] [95% CI][d]	[redacted]	[redacted]
Response ratio [95% CI][b]	[redacted]	
P-value[c]	[redacted]	

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
	[redacted]	
IRC-assessed response		
Best overall response, n (%)		
CR	[redacted]	[redacted]
Cri	[redacted]	[redacted]
NPR	[redacted]	[redacted]
PR	[redacted]	[redacted]
PRL	[redacted]	[redacted]
SD	[redacted]	[redacted]
Non-PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Discontinued prior to first assessment	[redacted]	[redacted]
Not assessed	[redacted]	[redacted]
Overall response rates		
ORR, n (%)[a] [95% CI][d]	[redacted]	[redacted]
Response ratio [95% CI][b]	[redacted]	
P-value[c]	[redacted]	

CI – Confidence interval; CR – Complete response; IRC – Independent Review Committee; ORR – Overall response rate; PD – Progressive disease; PR – Partial response; PRL – Partial response with lymphocytosis; SD – Stable disease.

[a] Responders are defined as patients with a best overall response of partial response or higher [b] Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.

[c] P-value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.

[d] Clopper-Pearson confidence interval.

Source: ALPINE CSR[76]

B.2b.6.2 Sensitivity analysis for the primary endpoint

As described in Table 37, exploratory sensitivity analyses were conducted, including counting the assessments of PR-L that were followed by PR or higher responses, confirming the robustness of the primary analysis.

Table 37: Results of the sensitivity analysis for the primary endpoint

Analysis	ORR, n (%) [95% CI]		ORR response ratio	
	Zanubrutinib (N=327)	Ibrutinib (N=325)	Response ratio (95% CI)	P-value (superiority)
Primary analysis	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis				
Based on per-protocol analysis set	[redacted]	[redacted]	[redacted]	[redacted]
PR-L subsequently followed by PR or higher counted as best OR of PR	[redacted]	[redacted]	[redacted]	[redacted]
Accounting for drug interruptions	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients who died due to COVID-19	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; ORR – Overall response rate; OR – overall response; PR – Partial response; PRL – Partial response with lymphocytosis; SD – Stable disease.
Source: ALPINE CSR[76]

B.2b.6.3 Secondary outcomes

Progression-free survival

At data cut-off of 01 December 2021, when compared to treatment with ibrutinib, treatment with zanubrutinib was associated with a 45% reduction in the risk of INV-assessed disease progression or death [redacted][76]

As shown in the KM plot presented in Figure 15, median PFS was not reached in either the zanubrutinib or ibrutinib arm with a median follow-up time of 22.1 months in both treatment arms. As reported in Table 38, the event-free rates for patients in the zanubrutinib and ibrutinib arms, respectively, were reported as [redacted]% and [redacted]% at 12 months and [redacted]% and [redacted]% at 24 months.[76]

Figure 15: Kaplan–Meier plot for INV-assessed PFS in ALPINE

INV – Investigator; PFS – Progression free survival.
Source: ALPINE CSR[76]

In line with the INV assessment of PFS, zanubrutinib demonstrated a statistically significant improvement in IRC-assessed PFS compared to ibrutinib after a median follow-up of 22.1 months in both arms. When compared to treatment with ibrutinib, treatment with zanubrutinib was associated with a statistically significant 39% reduction in the risk of disease progression or death [redacted][76]

As shown in the KM plot presented in Figure 16, median PFS was not reached in either the zanubrutinib or ibrutinib arm. The event-free rates for patients in the zanubrutinib and ibrutinib arms, respectively, were reported as [redacted]% and [redacted]% at 12 months and [redacted]% and [redacted]% at 24 months.[76]

Figure 16: Kaplan–Meier plot for IRC-assessed PFS in ALPINE

IRC – Independent Review Committee; PFS – Progression free survival.
Source: ALPINE CSR[76]

Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, showed statistically significant superior INV- and IRC-assessed PFS for zanubrutinib compared with ibrutinib (HR: 0.65; 95% CI: 0.49, 0.86; p =0.0024 for both INV- and IRC-assessed PFS), confirming the results of the 2021 data cut.[77] Median INV-assessed PFS was not reached in the zanubrutinib group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group.[77]

Table 38: IRC- and INV-assessed PFS in ALPINE

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
INV-assessed PFS, n (%) (DCO 01 December 2021)		
Events	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
HR (95% CI)[a] [p-value][b]	[redacted]	
Event-Free Rate at, % (95% CI)[c] (DCO 01 December 2021)		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
INV-assessed PFS, n (%) (DCO 08 August 2022)		
Events	87 (26.6)	118 (36.3)
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
HR (95% CI)[a] [p-value][b]	0.65 (0.49, 0.86); p=0.0024	
Median (95% CI) [months]	NE (34.3, NE)	34.2 (33.3, NE)
IRC-assessed PFS, n (%) (DCO 01 December 2021)		
Events	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
HR (95% CI)[a] [p-value][b]	[redacted]	
Event-Free Rate at, % (95% CI)[c] (DCO 01 December 2021)		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
IRC-assessed PFS, n (%) (DCO 08 August 2022)		
Events	88 (26.9)	120 (36.9)
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
HR (95% CI)[a] [p-value][b]	0.65 (0.49, 0.86); p=0.0024	

DCO – data cut-off; CI – Confidence interval; PFS – Progression-free survival; INV – investigator assessed; IRC – Independent review committee; NE – not estimable.
[a] HR is the ratio of the hazard of the zanubrutinib arm divided by that of the ibrutinib arm.
[b] Superiority 2-sided p-value.
[c] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: ALPINE CSR[76], Data on File, Brown et al.[77]

Duration of response

As of the data cut-off of 01 December 2021, [redacted] patients on zanubrutinib and [redacted] patients on ibrutinib either had progressive disease (INV-assessed) or had died. At a median follow-up of [redacted] and [redacted] months in the zanubrutinib and ibrutinib arms, respectively, median DOR was not reached. As reported in Table 39, the event-free rates for

patients in the zanubrutinib and ibrutinib arms, respectively, were reported as [redacted]% and [redacted]% at 12 months and [redacted]% and [redacted]% at 24 months.[76]

DOR determined by IRC-assessment was consistent to DOR determined by INV-assessment, with [redacted] patients on zanubrutinib and [redacted] patients on ibrutinib having either progressive disease (IRC-assessed) or had died at a median follow-up of 16.4 months and 13.8 months, respectively.[76]

Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, confirmed the results of the 2021 data cut, with more patients experiencing progressive disease (INV-assessed) or dying in the ibrutinib arm compared to the zanubrutinib arm (25.7% compared to 19.4%). Median DOR was not reached in the zanubrutinib group and was 33.9 months (95% CI, 33.9 to not estimable) in the ibrutinib group. DOR determined by IRC-assessment was consistent with DOR determined by INV-assessment in line with the results of the 2021 data cut.[77]

Table 39: INV and IRC-assessed DOR in ALPINE

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
INV-assessed DOR, n (%)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Median, (95% CI)[a]	[redacted]	[redacted]
Event free rate at, % (95% CI)[b]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
IRC-assessed DOR, n (%)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Median, (95% CI)[a]	[redacted]	[redacted]

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Event free rate at, % (95% CI)[b]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

CI – Confidence interval; DOR – Duration of response; INV – investigator assessed; IRC – Independent review committee; NE – not estimable.
[a]Medians and other quartiles of duration of response are estimated by Kaplan-Meier method with 95% CIs estimated using the
method of Brookmeyer and Crowley.
[b]Event-free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: ALPINE CSR[76]

Time to treatment failure

As shown in the KM plot presented in Figure 17, median TTTF was not reached for either zanubrutinib or ibrutinib at a median follow-up of 25.1 months in both arms. However, when compared to ibrutinib, treatment with zanubrutinib was associated with a statistically significant [redacted]% reduction in time to treatment failure [redacted] As described in Table 40, the event-free rates for patients in the zanubrutinib and ibrutinib arms, respectively, were reported as [redacted]% and [redacted]% at 12 months and [redacted]% and [redacted]% at 24 months.[76]

Table 40: TTTF in ALPINE

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Events, n (%)[a]	[redacted]	[redacted]
HR [95% CI][b]	[redacted]	
P-value	[redacted]	
Median follow-up, months (95% CI)[c]	[redacted]	[redacted]
Event free rate at, % (95% CI)[d]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

CI – Confidence interval; HR – Hazard ratio; TTTF – Time to treatment failure.
[a]Treatment failure is the discontinuation of study treatment for any reason.
[b]Hazard ratio is the ratio of the hazard of the zanubrutinib arm divided by that of the ibrutinib arm.

[c]Median follow-up time was estimated by the reverse Kaplan-Meier method
[d]Event-free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: ALPINE CSR[76]

Figure 17: Kaplan–Meier plot for TTTF in ALPINE

TTTF – Time to treatment failure.
Source: ALPINE CSR[76]

Overall survival

As expected for long-term chronic illness such as CLL, OS data from ALPINE remains immature. As per the data-cut off on 01 December 2021, [redacted] deaths had occurred in the zanubrutinib arm [redacted] and [redacted] had occurred in the ibrutinib arm [redacted] after a median follow up of 24.9 and 24.6 months, respectively. When compared to treatment with ibrutinib, treatment with zanubrutinib was associated with a [redacted] reduction in the risk of death [redacted][76]

As shown in the KM plot presented in Figure 18 and reported in Table 41, the event-free rates for patients in the zanubrutinib and ibrutinib arms, respectively, were reported as [redacted] versus [redacted] at 12 months, [redacted] and [redacted] at 24 months, and NE and [redacted] at 36 months.[76]

Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, demonstrated that the difference in number of deaths between zanubrutinib and ibrutinib further increased, further highlighting the improved outcomes on zanubrutinib. Furthermore, the HR (HR:0.76; 95% CI: 0.51, 1.11) is lower within narrow confidence interval compared to the 2021 DCO, suggesting that a statistically significantly improvement in OS may be demonstrated with more mature data.[77]

Figure 18: Kaplan–Meier plot for OS in ALPINE

OS – Overall survival.
Source: ALPINE CSR[76]

Table 41: OS in ALPINE

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Deaths, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)[a]	[redacted]	
Event-Free Rate at, % (95% CI)[b]		
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

CI – Confidence interval, NE – Not estimated; OS – Overall survival
[a] HR is the ratio of the hazard of the zanubrutinib arm divided by that of the ibrutinib arm.
[b] Event-free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: ALPINE CSR[76]

Patient reported outcomes

When using the EORTC QLQ-C30 instrument, the mean changes from baseline of key patient reported endpoints showed greater improvements in the zanubrutinib arm compared with the ibrutinib arm, with the exception of pain, which showed similar improvement between the arms. Similarly, mean change from baseline in the VAS scale showed a consistently better improvement in patients in the zanubrutinib arm compared with patients in the ibrutinib arm when using the EQ-5D-5L instrument. The mean change in baseline in EORTC QLQ-C30 is described in Table 42.[76]

Table 42: Mean change from baseline in EORTC QLQ-C30

PRO endpoint	Zanubrutinib, mean change from baseline (SD)		Ibrutinib, mean change from baseline (SD)	
	Cycle 7*	Cycle 13*	Cycle 7*	Cycle 13*
GHS/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Physical function	[redacted]	[redacted]	[redacted]	[redacted]
Role function	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]

GHS – Global health Status; PRO – Patient reported outcomes; SD – Standard deviation; QoL – Quality of life
*One cycle = 28 days
Note: Only patients with data at both baseline and the each postbaseline visit were included in the summary statistics for change from baseline.
Source: ALPINE CSR[76]

When using the EQ-5D-5L instrument, mean change from baseline in the VAS showed a consistently better improvement (Mean [SD]) in patients in the zanubrutinib arm compared with patients in the ibrutinib arm at Cycle 7 (Zanubrutinib: [redacted]; Ibrutinib: [redacted]) and Cycle 13 (Zanubrutinib: [redacted]; Ibrutinib: [redacted]).[76]

B.2b.7 Subgroup analysis: R/R CLL

As presented in Figure 19, for the primary endpoint of INV-assessed ORR, a higher ORR was observed in the zanubrutinib arm than the ibrutinib arm across key prespecified subgroups, including:

- **Patients with unmutated IGHV** showed a statistically significant improvement in ORR with zanubrutinib compared to ibrutinib (rate difference: [redacted])
- **Patients with del17p/ TP53 mutation** showed a statistically significant improvement in ORR with zanubrutinib compared to ibrutinib (rate difference: [redacted])
- **Patients with bulky disease** showed a numerical improvement in ORR with zanubrutinib compared to ibrutinib (rate difference: [redacted])
- **Patients with baseline β_2 microglobulin greater than 3.5 mg/L** showed a numerical improvement in ORR with zanubrutinib compared to ibrutinib (rate difference: [redacted])[76]

Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, confirmed the improvements in ORR by subgroup with no significant deviations observed from the results of the 2021 data cut.[77] Of note, statistically significant improvements were observed in subgroup analyses performed with data from DCO 08 August 2022 in patients aged ≥65 years, without 17p deletion/TP53 mutation status, without bulky disease, and Binet stage C when previously, only a numerical improvement had been demonstrated (DCO 2021).[77]

Figure 19: Forest plot of rate difference of ORR by INV in ALPINE

CLL – Chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; IgVH – Immunoglobulin heavy chain gene; ORR – Overall response rate; PS – Performance status; PFS – Progression-free survival; IRC – Independent review committee; LDH – Lactate dehydrogenase; LDi – Longest diameter; SLL – Small lymphocytic lymphoma; TP53 – Tumour protein P55; ULN – Upper limit of normal; VAF – Variant allele frequency
[a] Rate difference (zanubrutinib minus ibrutinib) and 95% confidence interval were unstratified for subgroups.
[b] Bulky disease of yes is derived from any target lesion longest diameter ≥ 5 cm.
Source: ALPINE CSR[76]

As presented in Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, confirmed the improvements in PFS by subgroup with no significant deviations observed from the results of the 2021 data cut.[77] Of note, statistically significant improvements were observed in subgroup analyses performed with data from DCO 08 August 2022 in patients with baseline ECOG ≥1 when previously, only a numerical improvement had been demonstrated (DCO 2021).[77]

Figure 20, for the secondary endpoint of INV-assessed PFS, HRs in favour of zanubrutinib compared to ibrutinib were observed across all key prespecified subgroups, including:

- **Patients with IGHV unmutated** showed a statistically significant improvement in PFS with zanubrutinib compared to ibrutinib [redacted]

- **Patients with del17p/ TP53 mutation** showed a statistically significant improvement in PFS with zanubrutinib compared to ibrutinib [redacted]

- **Patients with baseline β_2 microglobulin greater than 3.5 mg/L** showed a numerical improvement in PFS with zanubrutinib compared to ibrutinib [redacted]

- **Patients with bulky disease** showed a numerical improvement in PFS with zanubrutinib compared to ibrutinib [redacted][76]

Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, confirmed the improvements in PFS by subgroup with no significant deviations observed from the results of the 2021 data cut.[77] Of note, statistically significant improvements were observed in subgroup analyses performed with data from DCO 08 August 2022 in patients with baseline ECOG ≥1 when previously, only a numerical improvement had been demonstrated (DCO 2021).[77]

Figure 20: Forest plot of rate difference of PFS by INV in ALPINE

Source: ALPINE CSR[76]
CLL – Chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; IgVH – Immunoglobulin heavy chain gene; PS – Performance status; PFS – Progression-free survival; IRC – Independent review committee; LDH – Lactate dehydrogenase; LDi – Longest diameter; SLL – Small lymphocytic lymphoma; TP53 – Tumour protein P55; ULN – Upper limit of normal; VAF – Variant allele frequency.
[a] Hazard ratio and 95% CI were from a Cox regression model with the ibrutinib arm as the reference group. Estimates were unstratified for subgroups.
[b] Bulky disease of yes is derived from any target lesion longest diameter ≥ 5 cm.

B.2.8 Meta-analysis

All efficacy and safety data relevant to patients with untreated CLL are provided from two relevant RCTs, ELEVATE-TN for acalabrutinib and SEQUOIA for zanubrutinib and BR. In addition, all efficacy and safety data relevant to patients with R/R CLL are provided from

three relevant RCTs, ASCEND and ELEVATE-RR for acalabrutinib and ALPINE for zanubrutinib and ibrutinib. Therefore, it was not necessary to conduct a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

To date, there are no published head-to-head RCTs comparing the efficacy and safety of zanubrutinib with acalabrutinib or ibrutinib in previously untreated patients with CLL, nor are there any published head-to-head RCTs comparing the efficacy and safety of zanubrutinib with acalabrutinib in patients with R/R CLL.

In the absence of head-to-head data, an indirect treatment comparison (ITC) is required to estimate relative treatment effects. The network meta-analysis (NMA) methodology is typically used to generate comparative estimates. However, this technique relies on a common comparator arm to contrast relative effects between treatments across a network of linked studies.

Due to significant heterogeneity in the design and comparators selection in CLL clinical trials, matching-adjusted indirect comparison (MAIC) was deemed a more appropriate methodology in adjusting for cross-trial heterogeneity and avoiding basing comparative estimates on distant connection in a network of evidence, in line with previous technology appraisals in this patient population.[6,19,78] The MAIC approach was chosen over the simulated treatment comparison (STC) approach as deriving predictive equations for outcomes would have been challenging given low event counts due to immature data, which would have prevented the development of robust equations.

In the previously untreated population, estimates of comparative efficacy are required comparing:

- Zanubrutinib versus acalabrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR therapy
- Zanubrutinib versus acalabrutinib in previously untreated adults with CLL who have a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable
- Zanubrutinib versus ibrutinib in previously untreated adults with CLL who have a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable

In the R/R population, estimates of comparative efficacy are required comparing:

- Zanubrutinib versus acalabrutinib in adults with R/R CLL who have had at least one previous therapy

Following an SLR (see Appendix D for further details) and assessment of feasibility examining cross-trial similarities and differences, ELEVATE-TN was deemed the most appropriate trial to inform the efficacy of acalabrutinib in previously untreated patients within a MAIC. Due to the paucity of evidence for ibrutinib specifically reported in patients with 17p deletion and/or TP53 mutation, no publications were identified which reported both population characteristics and outcomes specifically for previously untreated patients with 'high-risk' factors treated with ibrutinib. To address the data limitations, data from the R/R setting from ALPINE was leveraged, supported by a naïve comparison, to inform the comparative efficacy of zanubrutinib versus ibrutinib.

In patients with R/R CLL, both ELEVATE-RR and ASCEND were identified as the most appropriate trials to inform the efficacy of acalabrutinib within a MAIC. Whilst the study design of the ASCEND trial was comparable to ALPINE and the ELEVATE-RR trial was conducted in patients with 'high-risk' factors (17p deletion or 11q deletion), the ELEVATE-RR trial allowed an anchored MAIC to be conducted due to the common comparator, ibrutinib. Table 43 provides an overview of the ITCs included within the submission.

Table 43: Summary of the methodology and populations of the ITCs included in the submission

Comparator	Population	Methodology	Zanubrutinib data source	Comparator data source
Previously untreated CLL				
Acalabrutinib	Previously untreated adults with CLL who are unsuitable for FCR and BR therapy	Unanchored MAIC as described in Section B.2.9.1 Indirect comparison for zanubrutinib versus acalabrutinib using ELEVATE-TN in previously untreated CLL	SEQUOIA trial, pooled zanubrutinib Cohort 1 (Arm A) and Cohort 2 (Arm C)[32]	ELEVATE-TN, acalabrutinib monotherapy arm[79]
	Previously untreated adults with CLL who have a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable			

Comparator	Population	Methodology	Zanubrutinib data source	Comparator data source
Ibrutinib	Previously untreated adults with CLL who have a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable	Head-to-head comparison using R/R data as a proxy, supported by a naïve comparison using Mato et al. (2018) in untreated patients with 17p deletion, as described in Section B.2.9.4.2 Indirect comparison for zanubrutinib versus ibrutinib in previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable	ALPINE trial, zanubrutinib arm (patients with 17p deletion or TP53 mutation only)[76]	ALPINE trial, ibrutinib arm (patients with 17p deletion or TP53 mutation only[76]
R/R CLL				
Acalabrutinib	Adults with R/R CLL who have had at least one previous therapy	Anchored MAIC as described in Section B.2.9.2 Indirect comparison for zanubrutinib versus acalabrutinib using ELEVATE-RR in R/R CLL	ALPINE trial, zanubrutinib arm[76]	ELEVATE-RR, acalabrutinib arm[56]
	Adults with R/R CLL who have had at least one previous therapy	Unanchored MAIC as described in Section B.2.9.3 Indirect comparison for zanubrutinib versus acalabrutinib using ASCEND	ALPINE trial, zanubrutinib arm[76]	ASCEND trial, acalabrutinib arm[80]

17p – chromosome 17; BR- Bendamustine-rituximab; CIT – Chemo-immunotherapy; CLL – chronic lymphocytic leukaemia; FCR – fludarabine-cyclophosphamide-rituximab; ITC – indirect treatment comparison; MAIC – Matching-adjusted indirect comparison. R/R – relapsed/refractory; TP53 – tumour protein 53

B.2.9.1 Indirect comparison for zanubrutinib versus acalabrutinib using ELEVATE-TN in previously untreated CLL

B.2.9.1.1 Methodology

A number of publications were identified reporting outcomes for ELEVATE-TN, of which, Sharman (2020) was deemed most appropriate given that the follow-up (median: 28.3 months) reported was most comparable with the follow-up available from the SEQUOIA trial (median: 26.35 months).[79] Table 44 compares the study design and eligibility criteria of ELEVATE-TN and SEQUOIA.

The MAIC approach used individual patient-level data (IPD) from the SEQUOIA trial. As baseline characteristics were not reported separately for patients with 17p mutation and patients without 17p deletion from the ELEVATE-TN trial, it was not possible to conduct a separate MAIC using the populations in Cohort 1 (arm A) and Cohort 2 (arm C) of SEQUOIA. As such, data for zanubrutinib from Cohort 1 (arm A) and Cohort 2 (arm C) of the SEQUOIA trial were pooled in order to create a cohort that included patients with and without 17p deletion to match the eligibility criteria for ELEVATE-TN. This approach was validated as appropriate by UK experts in attendance at an advisory board (03 November 2022) conducted by the Company.[11]

The pooled trial population was then adjusted to match the average baseline characteristics reported in the ELEVATE-TN trial for patients receiving acalabrutinib. The unadjusted population characteristics of the acalabrutinib monotherapy arm in the ELEVATE-TN study and pooled zanubrutinib population from the SEQUOIA study are presented in Table 45.

Table 44: SEQUOIA and ELEVATE-TN study design, inclusion, and exclusion criteria

	SEQUOIA	ELEVATE-TN
Study design		
Patient population	Previously untreated CD20-positive CLL or SLL who were deemed ineligible for FCR therapy	Previously untreated CD20-positive CLL
Phase	III	III
Study design	Randomised, open-label, international, multi-centre	Randomised, open-label, international, multi-centre
Follow-up	26.35 months (median)	28.3 months (median)
Treatment exposure	Cohort 1 (Arm A): 26.07 (median) Cohort 2 (Arm C): 30.00 (median)	27.7 months (median)

	SEQUOIA	ELEVATE-TN
Outcome definition		
Outcome assessment method	iwCLL IRC PFS (primary), iwCLL INV PFS, IRC ORR, INV ORR, OS, DOR	iwCLL IRC PFS iwCLL INV PFS, IRC ORR, INV ORR, OS, TTNT
Definition of PFS	PFS is defined as the time from date of randomisation to the date of first INV-assessed disease progression or death due to any cause	Time from date of randomisation to date of first INV-assessed DP or death from any cause
Definition of ORR	Achieving either a CR, CRi, nPR or PR (includes PR-L)	Achieving either a CR, CRi, nPR or PR (includes PR-L)
Inclusion criteria		
Demographics	≥65 years <65 years with CIRS >6, a creatinine clearance < 70 mL/min and history of previous serious infection or multiple infections in the past 2 years	≥65 years <65 years with CIRS >6 or a creatine clearance of 30-69 mL/min
Disease characteristics	Confirmed diagnosis of CD20-positive CLL ECOG performance status 0-2 Adequate bone marrow function Adequate organ function Measurable disease by CT/MRI Life expectancy ≥ 6 months	Confirmed diagnosis of CD20-positive CLL ECOG performance status 0-2 Adequate haematologic, hepatic, and renal function
Exclusion criteria		
Previous treatments	Previous systemic treatment for CLL/SLL Any live, attenuated vaccine within 4 weeks of first dose of study drug Required ongoing need for corticosteroid treatment	Previous systemic treatment for CLL Any live vaccine within 4 weeks of first dose of study drug Requires treatment with proton pump inhibitors
Prior conditions	Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation Clinically significant cardiovascular disease Prior malignancy within the past 3 years History of severe bleeding disorder Severe or debilitating pulmonary disease Active fungal, bacterial, and/or viral infection requiring systemic therapy Known CNS involvement by leukaemia or lymphoma	Known prolymphocytic leukaemia or history of Richter's transformation Clinically significant cardiovascular disease History of stroke or intracranial haemorrhage within 6 months before randomisation Known history of bleeding CNS lymphoma or leukaemia

CIRS – Cumulative illness rating score; CLL – Chronic lymphocytic leukaemia; CNS – Central nervous system; CR – Complete response; DOR – Duration of response; DP – Disease progression; ECOG – Eastern Cooperative Oncology group; FCR – Fludarabine-cyclophosphamide-rituximab; INV – Investigator; IRC – Independent Review Committee; iwCLL – International workshop on chronic lymphocytic leukaemia; ORR – Overall response rate; OS – Overall survival; PFS – Progression free survival; PS – Partial response; SLL – Small lymphocytic leukaemia.
Source: SEQUOIA CSR[75], Sharman 2020[79]

Table 45: Unadjusted population characteristics for acalabrutinib in ELEVATE-TN and zanubrutinib in SEQUOIA

Population Characteristics		ELEVATE-TN acalabrutinib monotherapy (N = 179)	SEQUOIA pooled zanubrutinib Cohort 1 (arm A) and Cohort 2 (arm C) (N = 352)
IGHV mutation	Mutated (vs. unmutated), %	33.50%	[redacted]
17p deletion and/or TP53 mutation	del17p only (vs. no del17p and no TP53 mutation), %	2.20%	[redacted]
	del17p and TP53 mutation (vs. no del17p and no TP53 mutation), %	6.70%	[redacted]
	TP53 mutation only (vs. no del17p and no TP53 mutation), %	3.90%	[redacted]
11q deletion	Yes (vs. no), %	17.30%	[redacted]
β_2-Microglobulin, mg/L	>3.5 (vs. ≤3.5), %	78.20%	[redacted]
Bulky disease, LDi in cm	≥5 (vs. <5), %	38.00%	[redacted]
Age, years	≥75 (vs. <65), %	27.90%	[redacted]
	≥65 and <75 (vs. <65), %	56.40%	[redacted]
	Median	70.00	[redacted]
Region	North America or Europe (vs. Others), %	88.30%	[redacted]
Sex	Male (vs. female), %	62.00%	[redacted]
Complex karyotype (≥3 abnormalities)	Yes (vs. no), %	17.30%	[redacted]
ECOG	1 (vs. 2), %	92.20%	[redacted]
Cancer type	CLL (vs. SLL), %	100.00%	[redacted]
Time from initial diagnosis, months	Median	24.40	[redacted]
Ethnicity	Hispanic or Latino (vs. other), %	6.60%	[redacted]
Creatinine clearance, mL/min	<60 (vs. ≥60), %	26.80%	[redacted]
	Median	75.00	[redacted]
Any cytopenia	Yes (vs. no), %	47.50%	[redacted]
Anaemia	Yes (vs. no), %	38.00%	[redacted]
Thrombocytopenia	Yes (vs. no), %	18.40%	[redacted]
Neutropenia	Yes (vs. no), %	5.60%	[redacted]
CLL-IPI	High or very high (vs. low or intermediate), %	87.50%	[redacted]
Rai Stage	II (vs. I), %	24.60%	[redacted]
	III (vs. I), %	27.90%	[redacted]
	IV (vs. I), %	20.70%	[redacted]

CLL – Chronic lymphocytic leukaemia; CLL-IPI – Chronic lymphocytic leukaemia international prognostic index; CIRS – Cumulative Illness Rating Scale; ECOG – Eastern Cooperative Oncology Group Performance Status Scale; ESS – Effective sample size; IGHV – Immunoglobulin heavy chain gene; ITT – Intention to treat; LDi – Longest diameter; PS – Performance status; SLL – Small lymphocytic lymphoma; TP53 – Tumour protein P53 gene.
Source: SEQUOIA CSR[75], Sharman 2020[79]

Derivation of individual patient level data

In addition to the population characteristics extracted from ELEVATE-TN, patient-level survival data (i.e., PFS and OS) were reconstructed from the published KM curves of ELEVATE-TN using NICE recommended methodology.[81]

Patient-level data were reconstructed from the clinical trial published KM curves using the Engauge Digitizer.[82] To ensure accuracy, the digitised curves were overlaid onto the original images and visually compared against the published curves. These coordinates were then used to generate reconstructed IPD (RIPD) (e.g., time and censoring status) for each curve using the method published in Guyot et al.[83] The KM curves derived from RIPD were overlaid onto the original image and visually compared against the published curves. Median survival and number at risk over time were examined to ensure close replication of the published results.

As IRC-assessed PFS was the primary endpoint in both SEQUOIA and ELEVATE-TN, PFS analyses were conducted using IRC-assessed PFS only.

Generating weights to balance average baseline characteristics

As ELEVATE-TN and SEQUOIA did not contain a common comparator arm, an unanchored MAIC was conducted following the NICE DSU guidelines and method described by Signorovitch et al.[84,85] This process involved three key steps:

1. Deriving balancing weights for patients in the pooled zanubrutinib population from SEQUOIA to match the key population characteristics, with prognostic or effect modifying potential, of the acalabrutinib arm in ELEVATE-TN using a logistic regression model.

2. Applying balancing weights derived in Step 1 to obtain adjusted outcomes for patients in the pooled zanubrutinib population from SEQUOIA to calculate the effective sample size (ESS).

3. Estimating the relative treatment effect between the re-weighted zanubrutinib population from SEQUOIA and the acalabrutinib population in ELEVATE-TN.

Further details of the MAIC methodology described in the steps above can be found in Appendix N.

The following baseline characteristics were considered to have a prognostic or effect modifying potential based on a review of published evidence:

- IGHV mutation (mutated vs. unmutated)
- Cytogenetic mutation (e.g., del17q, del11q, TP53 mutation)
- β2-microglobulin (e.g., >3.5 mg/L vs. ≤3.5 mg/L)
- Bulky disease (e.g., longest diameter [LDi] ≥5cm vs. LDi <5cm)
- Age group (e.g., <65 vs. 65-75 vs. >75)
- Geographic region (e.g., Europe vs. North America vs. Other)
- Sex (male vs. female)
- Complex karyotype (e.g., ≥3 vs. <3 abnormalities)
- ECOG performance score (e.g., 0 vs. 1 vs. 2)
- Cancer type (CLL vs. SLL)
- CLL staging (e.g. Rai stage)
- Time from initial diagnosis
- Ethnicity (Hispanic or Latino vs. other)
- Creatinine clearance (e.g., <60 mL/min vs. ≥60 mL/min)
- Any cytopenia (yes vs. no)
- Cytopenia types and associated haematology results (e.g., anaemia and haemoglobin count, thrombocytopenia and platelet count, and neutropenia and neutrophil count, and white blood cells count)
- CLL international prognostic index (IPI) (high or very high vs. low or intermediate)
- Lactate dehydrogenase (e.g., >250 U/L vs. ≤250 U/L)*
- B-symptoms including weight loss, fatigue, fever, or night sweats (yes vs. no)*
- Cumulative Illness Rating Scale (CIRS) standard or geriatric version (e.g., >6 or ≤6)*[1]

The population characteristics included in the MAIC analyses are presented in Table 46. Two matching models were considered in the analyses.

'Any cytopenia' or individual cytopenia types were removed from the list of matching factors due to multicollinearity issues when being included in the same model with Rai score. Furthermore, since complex karyotype was recorded with a high missing rate (approx. 47%) in the SEQUOIA study, it was also excluded from the list of matching factors. Feedback received from an advisory board conducted by the Company (03 November 2022) highlighted that complex karyotype would not need to be adjusted for as this could introduce

*Not included in MAIC as data not reported in ELEVATE-TN publications

bias as these patients are typically less healthy and reporting of complex karyotype can be inconsistent.[11]

For age and creatinine clearance both the proportions in ranges and medians were available for matching. However, to avoid further reduction of ESS, only the proportions were used, and medians were discarded. Since ethnicity was also recorded with a relatively high missing rate (approx. 9%) in the SEQUOIA study, the impact of excluding the variable was explored in Model 2.

Feedback received from an advisory board conducted by the Company (03 November 2022) stated that the ESS were sufficiently high in each of these matching models and the model choices were valid. Furthermore, the experts agreed that most of the key differentiators for BTKis were captured.[11]

Table 46: Matching models for pooled zanubrutinib populations in SEQUOIA versus acalabrutinib monotherapy population in ELEVATE-TN

Population Characteristics		Model 1	Model 2
IGHV mutation	Unmutated (vs. mutated), %	✓	✓
17p deletion and/or TP53 mutation	del17p only (vs. no del17p and no TP53 mutation), %	✓	✓
	del17p and TP53 mutation (vs. no del17p and no TP53 mutation), %	✓	✓
	TP53 mutation only (vs. no del17p and no TP53 mutation), %	✓	✓
11q deletion	Yes (vs. no), %	✓	✓
β_2-Microglobulin, mg/L	>3.5 (vs. ≤3.5), %	✓	✓
Bulky disease, LDi in cm	≥5 (vs. <5), %	✓	✓
Age, years	≥75 (vs. <65), %	✓	✓
	≥65 and <75 (vs. <65), %	✓	✓
	Median	-	-
Geographic Region	North America or Europe (vs. Others), %	✓	✓
Sex	Male (vs. female)	✓	✓
Complex karyotype (≥3 abnormalities)	Yes (vs. no)	-	-
ECOG PS	1 (vs. 2), %	✓	✓
Cancer type	CLL (vs. SLL)	✓	✓
Time from initial diagnosis	Median	✓	✓
Ethnicity	Hispanic or Latino (vs. other), %	✓	-
Creatinine clearance, mL/min	<60 (vs. ≥60), %	✓	✓
	Median	-	-
Any cytopenia	Yes (vs. no), %	-	-
Anaemia	Yes (vs. no), %	-	-
Thrombocytopenia	Yes (vs. no), %	-	-
Neutropenia	Yes (vs. no), %	-	-

Population Characteristics		Model 1	Model 2
CLL-IPI	High or very high (vs. low or intermediate), %	✓	✓
Rai Stage	II (vs. I), %	✓	✓
	III (vs. I), %	✓	✓
	IV (vs. I), %	✓	✓

CLL – Chronic lymphocytic leukaemia; CLL-IPI – Chronic lymphocytic leukaemia international prognostic index; CIRS – Cumulative Illness Rating Scale; ECOG – Eastern Cooperative Oncology Group Performance Status Scale; ESS – Effective sample size; IGHV – immunoglobulin heavy chain gene; LDi – Longest diameter; PS – Performance status; SLL – Small lymphocytic lymphoma; TN – Treatment-naïve; TP53 – Tumour protein P53 gene.

Estimating the relative treatment effect

The balancing weights were applied to the IPD data of the index study to estimate adjusted outcomes. For the time-to-event outcomes, the adjusted KM curves were estimated by a weighted KM analysis and plotted alongside the KM curves of the unadjusted population and the corresponding population in the comparator study to illustrate the direction and the magnitude of the shift due to the adjustment.

In order to estimate the relative treatment effect on the time-to-event efficacy outcomes between zanubrutinib and acalabrutinib, IPD from the SEQUOIA were combined with the RIPD of ELEVATE-TN. A Cox proportional hazard regression model was then fitted using the treatment indicator as a predictor to derive naïve estimates of comparative efficacy before population adjustment. A weighted Cox proportional hazard regression model was fitted to derive estimates of comparative effect after population adjustment. HRs along with 95% CI were reported both for the unweighted and weighted Cox proportional regression models to provide naïve and MAIC-adjusted estimate of the relative efficacy.

B.2.9.1.2 Results

The summary of the population characteristics after matching by weights generated from both Model 1 and Model 2 are presented in Table 47. After matching, all matched baseline characteristics were balanced (i.e., statistically equivalent) between the trials as demonstrated in the histograms of normalised weights which are presented in Figure 21 and Figure 22 for Model 1 and Model 2, respectively.

Table 47: Population characteristics of the acalabrutinib monotherapy population in the ELEVATE-TN study vs. zanubrutinib population in the SEQUOIA after matching

Population characteristics		Acalabrutinib (N = 179)	Zanubrutinib Model 1 (ESS = 107.5)	Zanubrutinib Model 2 (ESS = 124.5)
IGHV mutation	Unmutated (vs. mutated), %	33.50%	[redacted]	[redacted]
17p deletion and/or TP53 mutation	del17p only (vs. no del17p and no TP53 mutation), %	2.20%	[redacted]	[redacted]
	del17p and TP53 mutation (vs. no del17p and no TP53 mutation), %	6.70%	[redacted]	[redacted]
	TP53 mutation only (vs. no del17p and no TP53 mutation), %	3.90%	[redacted]	[redacted]
11q deletion	Yes (vs. no), %	17.30%	[redacted]	[redacted]
β_2-Microglobulin, mg/L	>3.5 (vs. ≤3.5), %	78.20%	[redacted]	[redacted]
Bulky disease, LDi in cm	≥5 (vs. <5), %	38.00%	[redacted]	[redacted]
Age, years	≥75 (vs. <65), %	27.90%	[redacted]	[redacted]
	≥65 and <75 (vs. <65), %	56.40%	[redacted]	[redacted]
	Median	*70.00*	[redacted]	[redacted]
Region	North America or Europe (vs. Others), %	88.30%	[redacted]	[redacted]
Sex	Male (vs. female), %	62.00%	[redacted]	[redacted]
Complex karyotype (≥3 abnormalities)	*Yes (vs. no), %*	*17.30%*	[redacted]	[redacted]
ECOG PS	1 (vs. 2), %	92.20%	[redacted]	[redacted]
Cancer type	CLL (vs. SLL), %	100.00%	[redacted]	[redacted]
Time from initial diagnosis	Median, months	24.40	[redacted]	[redacted]
Ethnicity	Hispanic or Latino (vs. other), %	6.60%	[redacted]	[redacted]
Creatinine clearance, mL/min	<60 (vs. ≥60), %	26.80%	[redacted]	[redacted]
	Median	*75.00*	[redacted]	[redacted]
Any cytopenia	*Yes (vs. no), %*	*47.50%*	[redacted]	[redacted]
Anaemia	*Yes (vs. no), %*	*38.00%*	[redacted]	[redacted]
Thrombocytopenia	*Yes (vs. no), %*	*18.40%*	[redacted]	[redacted]
Neutropenia	*Yes (vs. no), %*	*5.60%*	[redacted]	[redacted]
CLL-IPI	High or very high (vs. low or intermediate), %	87.50%	[redacted]	[redacted]
Rai stage	II (vs. I), %	24.60%	[redacted]	[redacted]
	III (vs. I), %	27.90%	[redacted]	[redacted]
	IV (vs. I), %	20.70%	[redacted]	[redacted]

CLL – Chronic lymphocytic leukaemia; CLL-IPI – Chronic lymphocytic leukaemia international prognostic index; CIRS – Cumulative Illness Rating Scale; ECOG – Eastern Cooperative Oncology Group Performance Status Scale; ESS – Effective sample size; IGHV – immunoglobulin heavy chain gene; PS –Performance status; SLL – Small lymphocytic lymphoma; TN – Treatment-naïve; TP53 – Tumour protein P53 gene.

Figure 21: Distribution of the normalized weights for MAIC comparing SEQUOIA and ELEVATE-TN – Model 1

ESS – Effective sample size; MAIC – Matching-adjusted indirect comparison.

Figure 22: Distribution of the normalized weights for MAIC comparing SEQUOIA and ELEVATE-TN – Model 2

ESS – Effective sample size; MAIC – Matching-adjusted indirect comparison

The MAIC results for PFS and OS both before and after matching are summarised in Table 48. In Model 1, there was no statistically significant difference in PFS-IRC between zanubrutinib and acalabrutinib ( ). Similarly, there was no statistically significant difference in OS between zanubrutinib and acalabrutinib ( ). The results of Model 2 were consistent with Model 1, demonstrating no

statistically significant difference between zanubrutinib and acalabrutinib in PFS-IRC ([redacted]) or OS ([redacted]).

Table 48: Summary of MAIC results for zanubrutinib vs acalabrutinib for patients with untreated CLL

	PFS (IRC)		OS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; CLL – Chronic lymphocytic leukaemia; HR – Hazard ratio; MAIC – Matching-adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival.

The KM curves of PFS-IRC for acalabrutinib and zanubrutinib (both pre- and post-adjustment) are presented for Model 1 and Model 2 are presented in Figure 23 and Figure 24, respectively. There is little change in the pre-matching and post-matching KMs for zanubrutinib suggesting that the populations in ELEVATE-TN and SEQUOIA were relatively well-balanced.

Figure 23: KM Analysis of PFS-IRC for MAIC comparing SEQUOIA and ELEVATE-TN – Model 1

IRC – Independent review committee; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

Figure 24: KM Analysis of PFS-IRC for MAIC comparing SEQUOIA and ELEVATE-TN – Model 2

IRC – Independent review committee; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

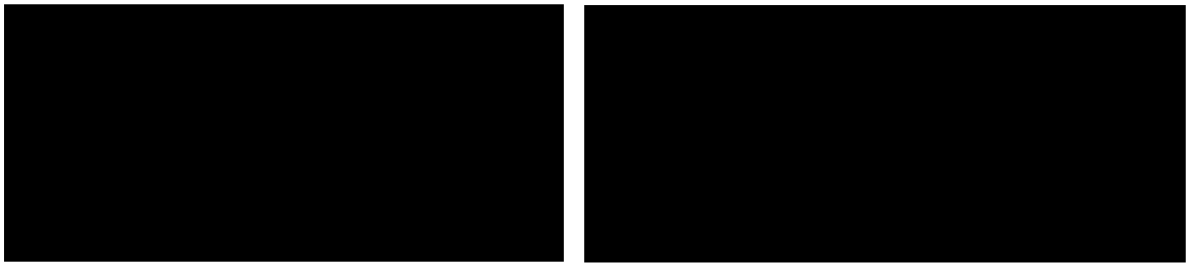
The MAIC demonstrates that zanubrutinib is at least non-inferior to acalabrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR therapy, in **patients both with and without 17p deletion**. Feedback received from an advisory board conducted by the Company (03 November 2022) agreed that the HRs were **clinically plausible** for PFS though noted that the CIs were wide due to immature data for long-term outcomes from SEQUOIA. In particular, the experts noted that the low number of deaths in SEQUOIA leads to high uncertainty in the relative OS estimates. Furthermore, the experts also noted that the unadjusted and adjusted KMs for PFS and OS were similar for zanubrutinib and acalabrutinib, supporting the non-inferiority of zanubrutinib to acalabrutinib.[11]

B.2.9.1.3 Assessment of proportional hazards

The log cumulative hazard plots and Schoenfeld residuals plots assessing the proportional hazards (PH) assumption for PFS-IRC after population adjustment are provided in Figure 25 and Figure 26, respectively. For both Model 1 and Model 2, the log cumulative hazard plots crossed at the beginning and remained reasonably parallel over the follow-up period. A potential violation of the proportionality was shown by slight convergence between the two curves towards the end of follow-up. However, the latter finding was not supported by the Schoenfeld residuals plots, which were nearly constant, meaning no time trend could be observed. In line with previous findings, formal hypothesis tests for proportionality did not detect the violation of PH assumption with a global Schoenfeld test p-value of [redacted] in

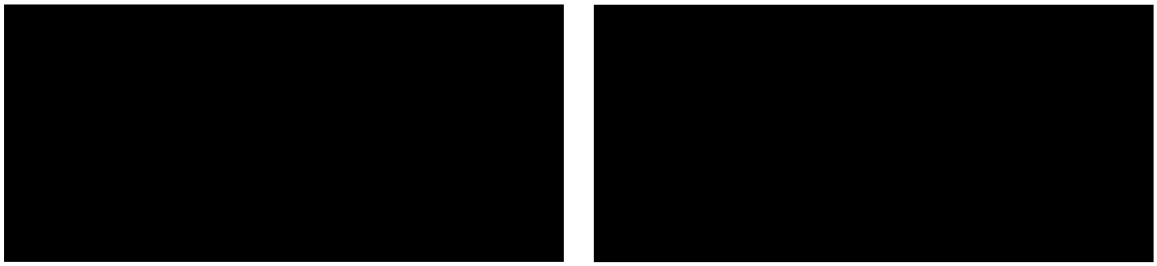
Model 1 and [redacted] in Model 2. Overall, no concerning evidence was identified against the PH assumption.

Figure 25: Log Cumulative Hazard Plot for PFS-IRC in the Model 1 (left panel) and Model 2 (right panel)



IRC – Independent review committee; PFS – Progression free survival.
Solid line = zanubrutinib, dashed line = acalabrutinib.

Figure 26: Schoenfeld Residual Plot for PFS-IRC in the Model 1 (left panel) and Model 2 (right panel)



IRC – Independent review committee; PFS – Progression free survival.

B.2.9.2 Indirect comparison for zanubrutinib versus acalabrutinib using ELEVATE-RR in R/R CLL

B.2.9.2.1 Methodology

Multiple publications were identified reporting outcomes for ELEVATE-RR, of which Byrd (2021) was deemed most appropriate. The follow-up reported (median: 40.9 months) was consistent across available publications for this trial, and hence is considered the most comparable to the ALPINE trial (median: 24.3 months).[56] Table 49 compares the study design and eligibility criteria of ELEVATE-RR and ALPINE.

Since the ELEVATE-RR study randomised patients only with 17p deletion or 11q deletion, the ITT population in the ALPINE study was restricted to the subset of 'high-risk' patients to ensure comparability across populations. The MAIC approach then used IPD from the

ALPINE trial and adjusted the ALPINE trial population to match the average baseline characteristics of the acalabrutinib arm in the ELEVATE-RR study. The unadjusted population characteristics of the acalabrutinib monotherapy arm in the ELEVATE-RR study compared to the population in the ALPINE study are presented in Table 49 below.

Table 49: ALPINE and ELEVATE-RR study design, inclusion and exclusion criteria

	ALPINE	ELEVATE-RR
Study design		
Patient population	Patients with a confirmed diagnosis of CLL or SLL that met the iwCLL criteria and had received at least one systemic therapy	Patients with previously treated CLL that met the iwCLL criteria and had received at least one systemic therapy
Phase	III	III
Study design	Randomised, open-label, international, multi-centre	Randomised, open-label, non-inferiority
Follow-up	24.3 months	40.9 months
Treatment exposure	23.8 months	38.3 months
Outcome definition		
Outcome assessment method	iwCLL INV ORR (primary) iwCLL IRC ORR, IRC PFS, INV PFS, DOR, TTTF, OS	iwCLL IRC PFS (primary), INV PFS, Number of patients with atrial fibrillation (secondary)
Definition of PFS	Time from randomisation to the date of first documentation of disease progression or death	Time from random assignment until disease progression or death from any cause
Definition of ORR	PR or higher, defined as CR, CRi, PR, nPR	N/A – not collected in the trial
Inclusion criteria		
Demographics	≥ 18 years	≥ 18 years
Disease characteristics	ECOG performance status 0-2 Adequate bone marrow function Adequate organ function	ECOG performance status 0-2 Presence of 17p deletion and/or 11q deletion confirmed by central laboratory testing
Exclusion criteria		
Previous treatments	Prior treatment with BTKi Any live, attenuated vaccine within 4 weeks of first dose of study drug	Prior BTK or BCL-2 inhibitor treatment Requires treatment with a strong CYP3A inhibitor/inducer Requires or receiving anticoagulation Prior allogeneic stem cell or autologous transplant Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days

	ALPINE	ELEVATE-RR
Prior conditions	Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation Clinically significant cardiovascular disease Prior malignancy within the past 3 years History of severe bleeding History or stroke or intracranial haemorrhage Severe pulmonary disease	Known CNS lymphoma or leukaemia Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenia purpura Significant cardiovascular disease History of severe bleeding History or stroke or intracranial haemorrhage Severe pulmonary disease

AE – Adverse event; CHF – Congestive heart failure; CIRS – Cumulative illness rating score; CLL – Chronic lymphocytic leukaemia; CR – Complete response; CVD – Cardiovascular disease; DOR – Duration of response; ECOG – Eastern Cooperative Oncology group; FCR – Fludarabine, cyclophosphamide and rituximab; IRC – Independent Review Committee; iwCLL – International workshop on chronic lymphocytic leukaemia; NYHA – New York Heart Association; ORR – Overall response rate; OS – Overall survival; PFS – Progression free survival; PS – Partial response; RR – Relapsed/refractory; SAE – Serious adverse event; SLL – Small lymphocytic leukaemia; BTK – Bruton's tyrosine kinase.
Source: ALPINE CSR[76], Byrd et al. [56]

Table 50: Unadjusted population characteristics for acalabrutinib in ELEVATE-RR and patients with 17p deletion and/or 11q deletion in ALPINE

Population characteristics		Active treatment arms		Control treatment arms	
		ELEVATE-RR acalabrutinib (N = 268)	ALPINE zanubrutinib (N = [redacted])	ELEVATE-RR ibrutinib (N = 265)	ALPINE ibrutinib (N = [redacted])
IGHV mutation	Unmutated (vs. mutated), %	17%	[redacted]	11%	[redacted]
Cytogenetic mutation subgroups by the presence of 17p deletion, 11q deletion, and TP53 mutation	Del17p, del11q and mutated TP53, %	5%	[redacted]	8%	[redacted]
	Del17p, no del11q, and mutated TP53, %	27%	[redacted]	29%	[redacted]
	Del17p, no del11q, and unmutated TP53, %	10%	[redacted]	5%	[redacted]
	Del17p, del11q, and unmutated TP53, %	3%	[redacted]	4%	[redacted]
	No del17p, del11q, and unmutated TP53, %	49%	[redacted]	49%	[redacted]
	No del17p, del11q, and mutated TP53, %	6%	[redacted]	6%	[redacted]
	Del17p, %	45%	[redacted]	45%	[redacted]
	Del11q, %	63%	[redacted]	66%	[redacted]
	TP53 Mutation, %	37%	[redacted]	42%	[redacted]
Complex karyotype (≥3 abnormalities)	Yes (vs. no), %	46%	[redacted]	47%	[redacted]
β_2-microglobulin, mg/L	>3.5 (vs. ≤3.5), %	78%	[redacted]	81%	[redacted]
Number of prior therapies	≥4 (vs. 1–3), %	12%	[redacted]	11%	[redacted]
Bulky disease, LDi in cm	≥5 (vs. <5), %	48%	[redacted]	51%	[redacted]
Age, years	≥75 (vs. <75), %	16%	[redacted]	16%	[redacted]
	Median	66.00	[redacted]	65.00	[redacted]
Sex	Male (vs. female), %	69%	[redacted]	73%	[redacted]
ECOG PS	2 (vs. 0-1), %	8%	[redacted]	8%	[redacted]
Binet stage (CLL patients only)*	A (vs. C), %	13%	[redacted]	12%	[redacted]
	B (vs. C), %	45%	[redacted]	43%	[redacted]

CLL – Chronic lymphocytic leukemia; CLL-IPI – Chronic lymphocytic leukemia international prognostic index; CIRS – Cumulative Illness Rating Scale; del11q/del13q – Deletion of the long arm of chromosome 11/13; del17p – Deletion of the short arm of chromosome 17; ECOG – Eastern Cooperative Oncology Group Performance Status Scale; ESS – Effective sample size; IGHV – Immunoglobulin heavy chain gene; LDi – Longest diameter; PS – Performance status; R/R – Relapsed/refractory; SLL – Small lymphocytic lymphoma; TP53 – Tumour protein P53 gene.
Source: ALPINE CSR[76], Byrd et al.[56]

Derivation of individual patient level data

In addition to the population characteristics extracted from ELEVATE-RR, patient-level survival data (i.e., PFS and OS) were reconstructed from the published KM curves of ELEVATE-RR using NICE recommended methodology.[81]

Patient-level data were reconstructed from the clinical trial published KM curves using the Engauge Digitizer.[82] To ensure accuracy, the digitised curves were overlaid onto the original images and visually compared against the published curves. These coordinates were then be used to generate RIPD (e.g., time and censoring status) for each curve using the method by Guyot et al.[83] The KM curves derived from RIPD were overlaid onto the original image and visually compared against the published curves. Median survival and number at risk over time were examined to ensure close replication of the published results.

Generating weights to balance average baseline characteristics

As ELEVATE-RR and ALPINE contained a common comparator arm (ibrutinib), an anchored MAIC was conducted following the NICE DSU guidelines and methods described by Signorovitch et al.[84,85] This process involved four key steps:

1. Deriving balancing weights for zanubrutinib patients in the ALPINE study to match the population characteristics of the acalabrutinib arm in the ELEVATE-RR study and deriving balancing weights for patients in the ibrutinib arm in the ALPINE study to match the population characteristics of the ibrutinib arm in the ELEVATE-RR study.

2. Applying balancing weights derived in Step 1 to obtain adjusted outcomes for patients in the zanubrutinib arm and ibrutinib treatment arms of ALPINE to calculate the ESS.

3. Estimating the relative treatment effect between the re-weighted zanubrutinib and ibrutinib arms in the reweighted population from ALPINE on the outcome of interest.

4. Estimating the relative treatment effect between zanubrutinib and acalabrutinib in ELEVATE-RR.

Further details of the MAIC methodology described in the steps above can be found in Appendix N.

The following baseline characteristics were considered to have a prognostic or effect modifying potential based on a review of published evidence:

- IGHV mutation (mutated vs. unmutated)
- Cytogenetic mutation (e.g., del17q, del11q, TP53 mutation)
- β2-microglobulin (e.g., >3.5 mg/L vs. ≤3.5 mg/L)
- Bulky disease (e.g., longest diameter [LDi] ≥5cm vs. LDi <5cm)
- Age group (e.g., <65 vs. 65-75 vs. >75)
- Geographic region (e.g., Europe vs. North America vs. Other)
- Sex (male vs. female)
- Complex karyotype (e.g., ≥3 vs. <3 abnormalities)
- ECOG performance score (e.g., 0 vs. 1 vs. 2)
- Cancer type (CLL vs. SLL)
- CLL staging (e.g. Rai stage)
- Time from initial diagnosis
- Ethnicity (Hispanic or Latino vs. other)
- Creatinine clearance (e.g., <60 mL/min vs. ≥60 mL/min)
- Any cytopenia (yes vs. no)
- Cytopenia types and associated haematology results (e.g., anaemia and haemoglobin count, thrombocytopenia and platelet count, and neutropenia and neutrophil count, and white blood cells count)
- Lactate dehydrogenase (e.g., >250 U/L vs. ≤250 U/L)
- B-symptoms including weight loss, fatigue, fever, or night sweats (yes vs. no)
- CIRS standard or geriatric version (e.g., >6 or ≤6)
- Number of prior therapies (1 vs. 2 vs. ≥3)
- Refractory status after the most recent therapy (refractory vs. relapsed disease)

The population characteristics included in the MAIC are presented in Table 51.

A matching model including all mutually available covariates with prognostic or effect modifying potential was explored but led to an insufficiently low ESS (ESS=31 for the zanubrutinib arm and ESS=25 in the ibrutinib arm). As such, to increase ESS, a matching model including only covariates considered effect modifiers was fitted and prognostic factors with effect modifying potential (age, sex, bulky disease, complex karyotype, and ECOG performance score) were excluded from the list of matching factors. The determination of

covariates as effect modifiers was based on internal clinical consultation and the choice of covariates included within the models was validated at an advisory board conducted by the Company (03 November 2022).[11]

Since there was a large imbalance in the proportion of patients with TP53 mutation across ELEVATE-RR and ALPINE populations, the impact of excluding the variable was explored in Model 2.

Table 51: Matching parameters for ALPINE vs. ELEVATE-RR

Population characteristics		Model 1	Model 2
IGHV mutation	Mutated (vs. unmutated), %	✓	✓
Cytogenetic mutation subgroups	Del17p, %	✓	✓
	Del11q, %	✓	✓
	TP53 Mutation, %	✓	-
Complex karyotype (≥3 abnormalities)	Yes (vs. no), %	-	-
β_2-microglobulin, mg/L	>3.5 (vs. ≤3.5), %	✓	✓
Number of prior therapies	≥4 (vs. 1–3), %	✓	✓
Bulky disease, LDi in cm	≥5 (vs. <5), %	-	-
Age, years	≥75 (vs. <75), %	-	-
	Median	-	-
Sex	Male (vs. female), %	-	-
Cancer type	CLL (vs. SLL)	✓	✓
ECOG PS	2 (vs. 0-1), %	-	-
Binet stage (CLL patients only)*	A (vs. C), %	✓	✓
	B (vs. C), %	✓	✓

CLL – Chronic lymphocytic leukaemia; del11q/del13q – Deletion of the long arm of chromosome 11/13; del17p – deletion of the short arm of chromosome 17; IGHV – Immunoglobulin heavy chain gene; LDi – Longest diameter; PS – Performance status; R/R – Relapsed/refractory; SLL – Small lymphocytic lymphoma; TP53 – Tumour protein P53 gene.

Feedback received from an advisory board conducted by the Company (03 November 2022) stated that the ESS were sufficiently high in each of these matching models and the model choices were valid. Furthermore, the experts when presented with the both Model 1 and Model 2, did not raise concerns regarding the appropriateness of the covariates included in the matching analysis.[11]

Estimating the relative treatment effect

The balancing weights were applied to the IPD data of the index study to estimate adjusted outcomes. For the time-to-event outcomes, the adjusted KM curves were estimated by a weighted KM analysis and plotted alongside the KM curves of the unadjusted population and

the corresponding population in the comparator study to illustrate the direction and the magnitude of the shift due to the adjustment.

The relative effect of zanubrutinib versus the control arm in ALPINE (ibrutinib) on the outcomes of interest was quantified along with 95% CI after applying the balancing weights to the patients included in ELEVATE-RR. As a last step, the indirect relative effect of zanubrutinib and comparator arm was obtained using the following formula, in the scale of the linear combination:

$$RE_{zanubrutinib\ vs.\ comparator} = RE_{\substack{zanubrutiniob\ vs.\ control \\ \text{in } the\ re-weighted\ index\ study}} - RE_{\substack{comparator\ vs.control \\ in\ the\ comparator\ study}}$$

B.2.9.2.2 Results

The summary of the population characteristics after matching by weights generated from both Model 1 and Model 2 are presented in Table 52 and Table 53. After matching, all matched baseline characteristics were balanced (i.e. statistically equivalent) between the trials as demonstrated in the histograms of normalised weights which are presented in Figure 27 and Figure 28 for Model 1 and Model 2, respectively.

Table 52: Population characteristics of the ELEVATE-RR study population vs. ALPINE study population before and after matching – Model 1

Population characteristics		Active treatment arms		Control treatment arms	
		Acalabrutinib (N = 268)	Zanubrutinib Model 1 (ESS = 79)	Ibrutinib (ELEVATE-RR) (N = 265)	Ibrutinib (ALPINE) (ESS = 63)
IGHV mutation	Mutated (vs. Unmutated), %	16.70%	[redacted]	10.60%	[redacted]
Cytogenetic mutation subgroups	Del17p, %	45.30%	[redacted]	45.30%	[redacted]
	Del11q, %	62.60%	[redacted]	66.10%	[redacted]
	TP53 Mutation, %	37.40%	[redacted]	42.30%	[redacted]
Complex karyotype (≥3 abnormalities)	*Yes (vs. no), %*	*46.30%*	[redacted]	*47.20%*	[redacted]
β_2-microglobulin, mg/L	>3.5 (vs. ≤3.5), %	78.10%	[redacted]	80.80%	[redacted]
Number of prior therapies	≥4 (vs. 1–3), %	12.40%	[redacted]	10.60%	[redacted]
Bulky disease, LDi in cm	*≥5 (vs. <5), %*	*47.80%*	[redacted]	*51.30%*	[redacted]
Age, years	*≥75 (vs. <75), %*	*16.40%*	[redacted]	*16.20%*	[redacted]
	Median	*66.00*	[redacted]	*65.00*	[redacted]

Population characteristics		Active treatment arms		Control treatment arms	
		Acalabrutinib (N = 268)	Zanubrutinib Model 1 (ESS = 79)	Ibrutinib (ELEVATE-RR) (N = 265)	Ibrutinib (ALPINE) (ESS = 63)
Sex	*Male (vs. female), %*	*69.00%*	[redacted]	*73.20%*	[redacted]
ECOG PS	*2 (vs. 0-1), %*	*7.50%*	[redacted]	*8.30%*	[redacted]
Cancer type	CLL (vs. SLL), %	100%	[redacted]	100%	[redacted]
Binet stage (CLL patients only)	A (vs. C), %	12.60%	[redacted]	11.60%	[redacted]
	B (vs. C), %	45.30%	[redacted]	42.60%	[redacted]

CLL – Chronic lymphocytic leukaemia; CLL-IPI – Chronic lymphocytic leukaemia international prognostic index; CIRS– Cumulative Illness Rating Scale; del11q/del13q – Deletion of the long arm of chromosome 11/13; del17p – Deletion of the short arm of chromosome 17; ECOG – Eastern Cooperative Oncology Group Performance Status Scale; ESS – Effective sample size; IGHV – Immunoglobulin heavy chain gene; PS – Performance status; R/R – Relapsed/refractory; SLL – Small lymphocytic lymphoma; TP53 – Tumor protein P53 gene.
Source: ALPINE CSR[76], Byrd et al.[56]

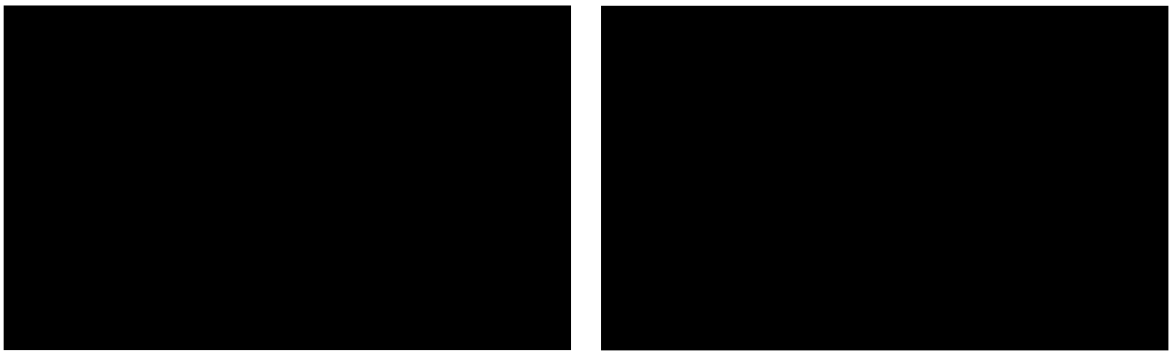
Table 53: Population characteristics of the ELEVATE-RR study population vs. ALPINE study population before and after matching – Model 2

Population characteristics		Active treatment arms		Control treatment arms	
		Acalabrutinib (N = 268)	Zanubrutinib Model 2 (ESS = 87)	Ibrutinib (ELEVATE-RR) (N = 265)	Ibrutinib (ALPINE) (ESS = 79)
IGHV mutation	Mutated (vs. Unmutated), %	16.70%	[redacted]	10.60%	[redacted]
Cytogenetic mutation subgroups	Del17p, %	45.30%	[redacted]	45.30%	[redacted]
	Del11q, %	62.60%	[redacted]	66.10%	[redacted]
	TP53 Mutation, %	*37.40%*	[redacted]	42.30%	[redacted]
Complex karyotype (≥3 abnormalities)	*Yes (vs. no), %*	*46.30%*	[redacted]	*47.20%*	[redacted]
β_2-microglobulin, mg/L	>3.5 (vs. ≤3.5), %	78.10%	[redacted]	80.80%	[redacted]
Number of prior therapies	≥4 (vs. 1–3), %	12.40%	[redacted]	10.60%	[redacted]
Bulky disease, LDi in cm	*≥5 (vs. <5), %*	*47.80%*	[redacted]	*51.30%*	[redacted]
Age, years	*≥75 (vs. <75), %*	*16.40%*	[redacted]	*16.20%*	[redacted]
	Median	*66.00*	[redacted]	*65.00*	[redacted]
Sex	*Male (vs. female), %*	*69.00%*	[redacted]	*73.20%*	[redacted]
ECOG PS	*2 (vs. 0-1), %*	*7.50%*	[redacted]	*8.30%*	[redacted]
Cancer type	CLL (vs. SLL), %	100%	[redacted]	100%	[redacted]
Binet stage (CLL patients only)*	A (vs. C), %	12.60%	[redacted]	11.60%	[redacted]
	B (vs. C), %	45.30%	[redacted]	42.60%	[redacted]

CLL – Chronic lymphocytic leukaemia; CLL-IPI – Chronic lymphocytic leukaemia international prognostic index; CIRS– Cumulative Illness Rating Scale; del11q/del13q – Deletion of the long arm of chromosome 11/13; del17p

– Deletion of the short arm of chromosome 17; ECOG – Eastern Cooperative Oncology Group Performance Status Scale; ESS – Effective sample size; IGHV – Immunoglobulin heavy chain gene; PS – Performance status; R/R – Relapsed/refractory; SLL – Small lymphocytic lymphoma; TP53 – Tumor protein P53 gene. Source: ALPINE CSR[76], Byrd et al.[56]

Figure 27: Distribution of the normalised weights for zanubrutinib (left) and ibrutinib (right) from MAIC comparing ALPINE and ELEVATE-RR – Model 1



ESS – Effective sample size; MAIC – Matching-adjusted indirect comparison.

Figure 28: Distribution of the normalised weights for zanubrutinib (left) and ibrutinib (right) from MAIC comparing ALPINE and ELEVATE-RR – Model 2

ESS – Effective sample size; MAIC – Matching-adjusted indirect comparison.

The MAIC results for PFS and OS both before and after matching are summarised in Table 54. Both IRC-PFS and INV-PFS were available from ELEVATE-RR, hence six MAICs in total were conducted.

In Model 1, there was no statistically significant difference in IRC-assessed PFS between zanubrutinib and acalabrutinib ( ) nor INV-assessed PFS ( ). Similarly, there is no statistically significant difference in OS between zanubrutinib and acalabrutinib ( ).

Consistent with Model 1, the results of Model 2 show there is no statistically significant difference between zanubrutinib and acalabrutinib in IRC-assessed PFS ([redacted]), INV-assessed PFS ([redacted]) or OS ([redacted]). Across all outcomes and models, zanubrutinib demonstrated a numerical improvement compared to acalabrutinib.

Table 54: Summary of MAIC results for zanubrutinib vs acalabrutinib for patients with R/R CLL – ELEVATE-RR

	PFS (IRC)		PFS (INV)		OS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; CLL – Chronic lymphocytic leukaemia; HR – Hazard ratio; MAIC – Matching-adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival.

The KM curves of IRC-assessed PFS for acalabrutinib and zanubrutinib (both pre- and post-adjustment) for Model 1 and Model 2 are presented in Figure 29 and Figure 30, respectively. Similarly, the KM curves of INV-assessed PFS for acalabrutinib and zanubrutinib (both pre- and post-adjustment) for Model 1 and Model 2 are presented in Figure 31 and Figure 32, respectively. Please note, the KM curves for zanubrutinib presented are the trimmed population of patients with 17p deletion and/or 11q deletion.

Figure 29: KM Analysis of PFS-IRC for MAIC comparing ALPINE and ELEVATE-RR – Model 1

IRC – Independent Review Committee; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

Figure 30: KM Analysis of PFS-IRC for MAIC comparing ALPINE and ELEVATE-RR – Model 2

IRC – Independent Review Committee; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

Figure 31: KM Analysis of PFS-INV for MAIC comparing ALPINE and ELEVATE-RR – Model 1

INV – Investigator; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

Figure 32: KM Analysis of PFS-INV for MAIC comparing ALPINE and ELEVATE-RR – Model 2

INV – Investigator; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

B.2.9.2.3 Assessment of proportional hazards

The log cumulative hazard plots and Schoenfeld residuals plots assessing the PH assumption after population adjustment are provided in Figure 33 and Figure 34 respectively for PFS-IRC and in Figure 35 and Figure 36, respectively for PFS-INV.

PFS-IRC

For Model 1, the log cumulative hazard plots were reasonably parallel before some convergence was displayed around the end of the study period. For Model 2, the curves remained parallel indicating no evidence of violation of the PH assumption either. Furthermore, the Schoenfeld residuals showed no evidence of a significant time trend over the study period. In line with previous findings, formal hypothesis tests for proportionality did not detect the violation of PH assumption with a global Schoenfeld test p-value of [redacted] for Model 1 and [redacted] for Model 2. Overall, no concerning evidence was identified against the PH assumption.

Figure 33: Log Cumulative Hazard Plot for PFS-IRC After Adjustment by Model 1 (Left Panel) and Model 2 (Right Panel)

IRC – Independent review committee; PFS – Progression free survival.
Solid line = zanubrutinib, dashed line = ibrutinib.

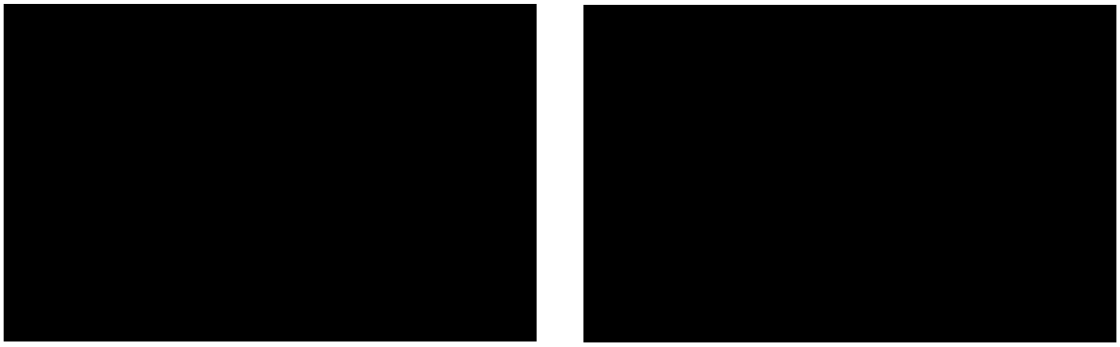
Figure 34: Schoenfeld Residual Plot for PFS-IRC After Adjustment by Model 1 (Left Panel) and Model 2 (Right Panel)

IRC – Independent review committee; PFS – Progression free survival.
Solid line = zanubrutinib, dashed line = ibrutinib.

PFS-INV

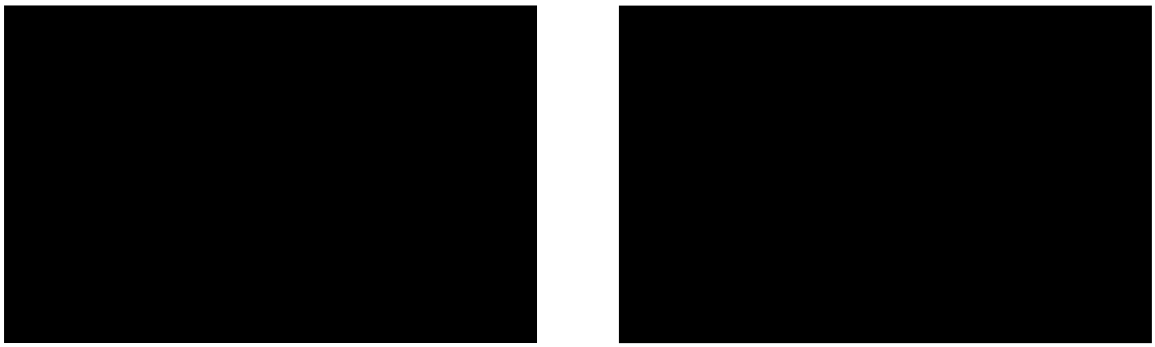
For Model 1, the log cumulative hazard plots were reasonably parallel before some convergence was displayed around the end of the study period. For Model 2, the curves remained parallel indicating no evidence of violation of the PH assumption either. Furthermore, the Schoenfeld residuals showed no evidence of a significant time trend over the study period. In line with previous findings, formal hypothesis tests for proportionality did not detect the violation of PH assumption with a global Schoenfeld test p-value of [redacted] for Model 1 and [redacted] for Model 2. Overall, no concerning evidence was identified against the PH assumption.

Figure 35: Log Cumulative Hazard Plot for PFS-INV After Adjustment by Model 1 (Left Panel) and Model 2 (Right Panel)



INV – Investigator-assessed; PFS – Progression free survival.
Solid line = zanubrutinib, dashed line = ibrutinib.

Figure 36: Schoenfeld Residual Plot for PFS-INV After Adjustment by Model 1 (Left Panel) and Model 2 (Right Panel)



INV – Investigator-assessed; PFS – Progression free survival.
Solid line = zanubrutinib, dashed line = ibrutinib.

B.2.9.3 Indirect comparison for zanubrutinib versus acalabrutinib using ASCEND in R/R CLL

B.2.9.3.1 Methodology

Multiple publications were identified reporting outcomes for ASCEND, of which Ghia (2020), was deemed most appropriate given that the follow-up (median: 16.1 months) reported was most comparable with the follow-up available from the ALPINE trial (median: 24.3 months).[86] Whilst Jacob et al. 2021 reported a median follow up of 22.0 months, no survival curves were reported and so a MAIC was not possible using this publication.[87] Table 55 compares the study design and eligibility criteria of ASCEND and ALPINE.

The MAIC approach used IPD from the ALPINE trial for zanubrutinib which was adjusted to match the baseline characteristics of the acalabrutinib arm of the ASCEND study. The unadjusted population characteristics of the acalabrutinib arm in the ASCEND study compared to zanubrutinib arm in the ALPINE study are presented in Table 56.

Table 55: ALPINE and ASCEND study design, inclusion, and exclusion criteria

	ALPINE	ASCEND
Study design		
Patient population	Patients with a confirmed diagnosis of CLL or SLL that met the iwCLL criteria and had received at least one systemic therapy	Patients with previously treated CLL and had received at least one systemic therapy
Phase	Phase 3	Phase 3
Study design	Randomised, open-label, international, multi-centre	Randomised, open-label, international, multi-centre
Follow-up	24.3 months	16.1 months
Treatment exposure	23.8 months	15.7 months
Outcome definition		
Outcome assessment method	iwCLL INV ORR (primary) iwCLL IRC ORR, IRC PFS, INV PFS, DOR, TTTF, OS	iwCLL IRC PFS (primary) iwCLL IRC ORR, INV ORR, INV PFS, DOR, OS, TTNT
Definition of PFS	Time from randomisation to the date of first documentation of disease progression or death	Time from random assignment until disease progression or death from any cause
Definition of ORR	PR or higher, defined as CR, CRi, PR, nPR	PR or higher, defined as CR, CRi, PR, nPR
Inclusion criteria		
Demographics	≥ 18 years	≥ 18
Disease characteristics	ECOG performance status 0-2 Adequate bone marrow function Adequate organ function	ECOG performance status 0-2 Adequate hepatic, hematologic and renal function.
Exclusion criteria		
Previous treatments	Prior treatment with BTKi Any live, attenuated vaccine within 4 weeks of first dose of study drug	Prior BTK or BCL-2 inhibitor treatment Any live, attenuated vaccine within 4 weeks of first dose of study drug Prior allogeneic stem cell or autologous transplant Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days Requires treatment with a strong CYP3A inhibitor/inducer

	ALPINE	ASCEND
		Requires or receiving proton pump inhibitors
Prior conditions	Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation Clinically significant cardiovascular disease Prior malignancy within the past 3 years History of severe bleeding History or stroke or intracranial haemorrhage Severe pulmonary disease	Known CNS lymphoma or leukaemia Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenia purpura Significant cardiovascular disease Prior malignancy History of bleeding diathesis History or stroke or intracranial haemorrhage Severe pulmonary disease History or stroke or intracranial haemorrhage

AE – Adverse event; BTK – Bruton's tyrosine kinase; CHF – Congestive heart failure; CIRS – Cumulative illness rating score; CLL – Chronic lymphocytic leukaemia; CR – Complete response; CVD – Cardiovascular disease; DOR – Duration of response; ECOG – Eastern Cooperative Oncology group; FCR – Fludarabine, cyclophosphamide and rituximab; IRC – Independent Review Committee; iwCLL – International workshop on chronic lymphocytic leukaemia; NYHA – New York Heart Association; ORR – Overall response rate; OS – Overall survival; PFS – Progression free survival; PS – Partial response; SAE – Serious adverse event; SLL – Small lymphocytic leukaemia; SYK – Spleen tyrosine kinase.
Source: ALPINE CSR[76], Ghia et al. 2020[86]

Table 56: Unadjusted population characteristics for acalabrutinib in ASCEND and zanubrutinib in ALPINE

Population Characteristics		ASCEND acalabrutinib (N = 155)	ALPINE zanubrutinib (N = 327)
IGHV mutation	Unmutated (vs. mutated), %	23.9%	[redacted]
Cytogenetic mutation subgroups	Del17p, %	18.1%	[redacted]
	Del11q, %	25.2%	[redacted]
	TP53 mutation, %	25.2%	[redacted]
Number of prior therapies	2, %	25.8%	[redacted]
	3, %	11.0%	[redacted]
	≥4, %	10.3%	[redacted]
Bulky disease, LDi in cm	≥ 5 (vs. <5), %	49.0%	[redacted]
Age, years	≥ 75 (vs. <75), %	21.9%	[redacted]
Sex	Male (vs. female), %	69.7%	[redacted]
Geographic Region	United States and Canada (vs. Europe), %	5.2%	[redacted]
	Australia and New Zealand (vs. Europe), %	5.8%	[redacted]

Population Characteristics		ASCEND acalabrutinib (N = 155)	ALPINE zanubrutinib (N = 327)
	Asia (vs. Europe), %	4.5%	[redacted]
Rai stage	III-IV (vs.0-II), %	41.9%	[redacted]
ECOG PS	0 (vs. ≥1), %	37.4%	[redacted]
Prior therapy	Purine analogue, %	70.3%	[redacted]
	Anti-CD20 antibody, %	83.9%	[redacted]
	Alkylators other than bendamustine, %	85.8%	[redacted]
	Bendamustine, %	30.3%	[redacted]

IGHV – Immunoglobulin heavy chain gene; LDi – Longest diameter; ECOG PS – Eastern Cooperative Oncology Group Performance Status.

Derivation of individual patient level data

In addition to the population characteristics extracted from ASCEND, patient-level survival data (i.e., PFS and OS) were reconstructed from the published KM curves of ASCEND using NICE recommended methodology.[81]

Patient-level data were reconstructed from the clinical trial published KM curves using the Engauge Digitizer.[82] To ensure accuracy, the digitised curves were overlaid onto the original images and visually compared against the published curves. These coordinates were then be used to generate RIPD (e.g., time and censoring status) for each curve using the method by Guyot et al.[83] The KM curves derived from RIPD were overlaid onto the original image and visually compared against the published curves. Median survival and number at risk over time were examined to ensure close replication of the published results.

As IRC-assessed PFS was the primary endpoint in ASCEND and a key secondary endpoint in ALPINE, all PFS analyses were conducted using IRC-assessed PFS only.

Generating weights to balance average baseline characteristics

As ASCEND and ALPINE did not contain a common comparator arm, an unanchored MAIC was conducted following the NICE DSU guidelines and methods described by Signorovitch et al.[84,85] This process involved three key steps:

1. Deriving balancing weights for patients in the zanubrutinib arm of ALPINE to match the key population characteristics, with prognostic or effect modifying potential, of the acalabrutinib arm in ASCEND using a logistic regression model.

2. Applying balancing weights derived in Step 1 to obtain adjusted outcomes for patients in the zanubrutinib arm in ALPINE to calculate the ESS.

3. Estimating the relative treatment effect between the re-weighted zanubrutinib population from ALPINE and the acalabrutinib population in ASCEND.

Further details of the MAIC methodology described in the steps above can be found in Appendix N.

The following baseline characteristics were considered to have a prognostic or effect modifying potential based on a review of published evidence:

- IGHV mutation (mutated vs. unmutated)
- Cytogenetic mutation (e.g., del17q, del11q, TP53 mutation)
- β2-microglobulin (e.g., >3.5 mg/L vs. ≤3.5 mg/L)
- Bulky disease (e.g., longest diameter [LDi] ≥5cm vs. LDi <5cm)
- Age group (e.g., <65 vs. 65-75 vs. >75)
- Geographic region (e.g., Europe vs. North America vs. Other)
- Sex (male vs. female)
- Complex karyotype (e.g., ≥3 vs. <3 abnormalities)
- ECOG performance score (e.g., 0 vs. 1 vs. 2)
- Cancer type (CLL vs. SLL)
- CLL staging (e.g. Rai stage)
- Time from initial diagnosis
- Ethnicity (Hispanic or Latino vs. other)
- Creatinine clearance (e.g., <60 mL/min vs. ≥60 mL/min)
- Any cytopenia (yes vs. no)
- Cytopenia types and associated haematology results (e.g., anaemia and haemoglobin count, thrombocytopenia and platelet count, and neutropenia and neutrophil count, and white blood cells count)
- Lactate dehydrogenase (e.g., >250 U/L vs. ≤250 U/L)
- B-symptoms including weight loss, fatigue, fever, or night sweats (yes vs. no)
- CIRS standard or geriatric version (e.g., >6 or ≤6)
- Number of prior therapies (1 vs. 2 vs. ≥3)
- Refractory status after the most recent therapy (refractory vs. relapsed disease)

A matching model including all mutually available covariates with prognostic or effect modifying potential was explored. To increase sample size, a matching model including only covariates considered effect modifiers was fitted and prognostic factors with effect modifying potential (age, sex, bulky disease, geographical region, ECOG performance score) were excluded from the list of matching factors. The determination of covariates as effect modifiers was based on internal clinical consultation and UK clinical experts in attendance at an advisory board (03 November 2022) conducted by the Company. As adjusting for covariates with either prognostic or effect modifying potential (Model 2) or effect modifying potential alone (Model 1) did not have a large impact on sample size, the impact of the additional adjustment was explored.

Table 57: Matching parameters for ALPINE versus ASCEND

Population characteristics		Model 1	Model 2
IGHV mutation	Unmutated (vs. mutated), %	✓	✓
Cytogenetic mutation subgroups	Del17p, %	✓	✓
	Del11q, %	✓	✓
	TP53 Mutation, %	✓	✓
Number of prior therapies	2, %	✓	✓
	3, %	✓	✓
	≥4,%	✓	✓
Bulky disease	LDi in cm, 5 (vs. <5)	-	✓
Age	75 (vs. <75)	-	✓
Sex	Male (vs. female), %	-	✓
Geographic region	US and Canada (vs. Europe)	-	✓
	Australia and New Zealand (vs. Europe)	-	✓
	Asia (vs. Europe)	-	✓
Rai stage III-IV	(vs. 0-II), %	✓	✓
ECOG performance status	2 (vs. 0-1), %	-	-
Prior therapy	Purine analogue, %	-	-
	Anti-CD20 antibody, %	-	-
	Alkylators other than bendamustine, %	-	-
	Bendamustine, %	-	-

ECOG – European Cooperative Oncology Group; IGHV – immunoglobulin heavy chain gene; LDi – Longest diameter.

Estimating the relative treatment effect

The balancing weights were applied to the IPD data of the index study to estimate adjusted outcomes. For the time-to-event outcomes, the adjusted KM curves were estimated by a weighted KM analysis and plotted alongside the KM curves of the unadjusted population and the corresponding population in the comparator study to illustrate the direction and the magnitude of the shift due to the adjustment.

In order to estimate the relative treatment effect on the time-to-event efficacy outcomes between the zanubrutinib and acalabrutinib, IPD from the ALPINE were combined with the RIPD of ASCEND. A Cox proportional hazard regression model was then fitted using the treatment indicator as a predictor to derive naïve estimates of comparative efficacy before population adjustment. A weighted Cox proportional hazard regression model was fitted to derive estimates of comparative effect after population adjustment. HRs along with 95% CI were reported both for the unweighted and weighted Cox proportional regression models to provide naïve and MAIC-adjusted estimate of the relative efficacy.

B.2.9.3.2 Results

The summary of the population characteristics after matching by weights generated from both Model 1 and Model 2 are presented in Table 58. After matching, all matched baseline characteristics were balanced (i.e. statistically equivalent) between the trials as demonstrated in the histograms of normalised weights which are presented in Figure 37 and Figure 38 for Model 1 and Model 2, respectively.

Table 58: Population characteristics of the ASCEND study population vs. ALPINE study population after matching

Population characteristics		Acalabrutinib (N = 155)	Zanubrutinib Model 1 (ESS = 143)	Zanubrutinib Model 2 (ESS = 103)
IGHV mutation	Unmutated (vs. mutated), %	23.9%	[redacted]	[redacted]
Cytogenetic mutation subgroups	Del17p, %	18.1%	[redacted]	[redacted]
	Del11q, %	25.2%		
	TP53 Mutation, %	25.2%		
Number of prior therapies	2, %	25.8%		
	3, %	11%		
	≥4,%	10.3%	[redacted]	[redacted]
Bulky disease	LDi in cm, 5 (vs. <5)	49.0%		
Age	75 (vs. <75)	21.9%		
Sex	Male (vs. female), %	69.7%		
Geographic region	US and Canada (vs. Europe)	5.2%		
	Australia and New Zealand (vs. Europe)	5.8%	[redacted]	[redacted]
	Asia (vs. Europe)	4.5%	[redacted]	[redacted]
Rai stage III-IV	(vs. 0-II), %	41.9%		
ECOG PS	2 (vs. 0-1), %	37.4%		
Prior therapy	Purine analogue, %	70.3%		
	Anti-CD20 antibody, %	83.9%		
	Alkylators other than bendamustine, %	85.8%	[redacted]	[redacted]
	Bendamustine, %	30.3%	[redacted]	[redacted]

ECOG PS – European Cooperative Oncology Group performance status; IGHV – immunoglobulin heavy chain gene; LDi – Longest diameter.
Source: ALPINE CSR[76], Ghia et al. 2020[86]

Figure 37: Distribution of the normalised weights for MAIC comparing ALPINE and ASCEND – Model 1

ESS – Effective sample size; MAIC – Matching-adjusted indirect comparison.

Figure 38: Distribution of the normalised weights for MAIC comparing ALPINE and ASCEND – Model 2

ESS – Effective sample size; MAIC – Matching-adjusted indirect comparison.

The MAIC results for PFS and OS both before and after matching are summarised in Table 59.

In Model 1, there was no statistically significant difference in IRC-assessed PFS between zanubrutinib and acalabrutinib ( ). Similarly, there no statistically significant difference in OS between zanubrutinib and acalabrutinib ( ). The results of Model 2 were consistent with Model 1, demonstrating no statistically

significant difference between zanubrutinib and acalabrutinib in IRC PFS ([redacted]) or OS ([redacted]).

Table 59: Summary of MAIC results for zanubrutinib vs acalabrutinib for patient's R/R CLL

	PFS (IRC)		OS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]

CLL – Chronic lymphocytic leukaemia; OS – Overall survival; PFS – Progression free survival; R/R – Relapsed/refractory.

The KM curves of PFS-IRC for acalabrutinib and zanubrutinib (both pre- and post-adjustment) are presented for Model 1 and Model 2 are presented in Figure 39 and Figure 40, respectively. There is little change in the pre-matching and post-matching KMs for zanubrutinib suggesting that the populations in ALPINE and ASCEND were relatively well-balanced.

Figure 39: KM Analysis of PFS-IRC for MAIC comparing ALPINE and ASCEND – Model 1

IRC – Independent Review Committee; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

Figure 40: KM Analysis of PFS-IRC for MAIC comparing ALPINE and ASCEND – Model 2

IRC – Independent Review Committee; MAIC – Matching-adjusted indirect comparison; PFS – Progression free survival.

B.2.9.3.3 Assessment of proportional hazards

The log cumulative hazard plots and Schoenfeld residuals plots assessing the PH assumption for the PFS-IRC after population adjustment are provided in Figure 41 and Figure 42, respectively. For both Model 1 and Model 2, the log cumulative hazard plots crossed multiple times suggesting that the PH assumption does not hold. However, the Schoenfeld residuals plots were nearly constant, meaning no time trend could be observed. Furthermore, formal hypothesis tests for proportionality did not detect the violation of PH assumption with a global Schoenfeld test p-value of [redacted] in Model 1 and [redacted] in Model 2. Overall, no concerning evidence was identified against the PH assumption.

Figure 41: Log Cumulative Hazard Plot for PFS-IRC in the Model 1 (left panel) and Model 2 (right panel)

IRC – Independent Review Committee; PFS – progression-free survival.
Solid line = zanubrutinib, dashed line = acalabrutinib.

Figure 42: Schoenfeld Residual Plot for PFS-IRC in the Model 1 (left panel) and Model 2 (right panel)

IRC – Independent Review Committee; PFS – progression-free survival.

B.2.9.4 Discussion

B.2.9.4.1 Indirect comparison for zanubrutinib versus acalabrutinib in previously untreated adults with CLL

A MAIC comparing zanubrutinib with acalabrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR therapy, both with and without 17p deletion was conducted. Following an SLR (Appendix D) and assessment of feasibility, no publications for acalabrutinib were identified which reported population characteristics and outcomes specifically for previously untreated patients with or without 17p deletion. As such, there was insufficient data to conduct an ITC separately for these populations.

The MAIC was conducted using pooled data for zanubrutinib from Cohort 1 (arm A) and Cohort 2 (arm C) of the SEQUOIA trial to match the available evidence from ELEVATE-TN. Upon matching, [redacted]% of the populations were patients with both a 17p deletion and TP53 mutation, [redacted]% had a 17p deletion only and [redacted]% had a TP53 mutation only, and therefore can be considered 'high-risk'.

Cohort 2 of SEQUOIA is among the largest bodies of prospective evidence collected specifically for patients with a 17p deletion and demonstrated consistent outcomes to treatment with zanubrutinib in patients without 17p deletion (comparable to outcomes of arm A in Cohort 1). Similarly, as demonstrated in ELEVATE-TN, the treatment effect in patients with and without 17p deletion were comparable, meaning the MAIC results are likely reflective of the relative efficacy of zanubrutinib versus acalabrutinib across both populations (previously untreated 'unfit' and 'high-risk').[79]

In TA429 and TA689, NICE provided a recommendation for acalabrutinib and ibrutinib, respectively, in previously untreated adults with CLL who have a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable based on data presented in previously treated patients.[78,88] Data from RESONATE and ASCEND were used as a proxy to support the reimbursement decisions in this population. Two MAICs have been conducted comparing outcomes with zanubrutinib versus acalabrutinib in patients with R/R CLL as described in Section B.2.9.2 Indirect comparison for zanubrutinib versus acalabrutinib using ELEVATE-RR in R/R CLL and B.2.9.3 Indirect comparison for zanubrutinib versus acalabrutinib using ASCEND. These analyses demonstrated that zanubrutinib is at least non-inferior to acalabrutinib in patients with R/R CLL. As the MAICs conducted using ELEVATE-RR and ASCEND contained a high proportion of patients with 17p deletion or TP53 mutation (~40% in each study), these analyses are deemed highly relevant as a proxy for previously untreated patients with 17p deletion or TP53 mutation.

The MAICs presented make the best use of the available evidence for zanubrutinib and acalabrutinib**.** The MAIC conducted in the previously untreated population, coupled with MAICs conducted in the R/R population, support the conclusion that zanubrutinib is at least non-inferior to acalabrutinib across both the previously untreated ‘unfit’ and ‘high-risk’ populations.

B.2.9.4.2 Indirect comparison for zanubrutinib versus ibrutinib in previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable

Ibrutinib is only approved by NICE in previously untreated 'high-risk’ patients with CLL.[88] There is a paucity of evidence specifically reported in patients with 17p deletion and/or TP53 mutation. Following an SLR (Appendix D) and assessment of feasibility, no publications were identified which reported both population characteristics and outcomes specifically for previously untreated patients with ‘high-risk’ factors treated with ibrutinib.

The key phase 3 trials for ibrutinib, ALLIANCE and RESONATE-2, were conducted in populations that were more representative of the ‘unfit’ patients and so were not representative of the ‘high-risk’ population – the population in which ibrutinib is approved by NICE. In the ALLIANCE trial, only 8.9% of patients had a TP53 mutation and 5.0% of patients had 17p deletion and in the RESONATE-2 trial, only 9.7% of patients had a TP53 mutation and patients with 17p deletion were excluded from the trial.[57,79] As such, there was

insufficient data to conduct an MAIC versus ibrutinib in the previously untreated 'high-risk' population. This conclusion was supported by UK experts in attendance at an advisory board (03 November 2022) held by the Company.[11]

With data in patients with R/R CLL having been previously accepted by NICE as a proxy to support reimbursement decisions in this population, head-to-head results comparing zanubrutinib with ibrutinib from the ALPINE trial were deemed highly relevant in this population.[78,88]

As presented in Table 38, zanubrutinib is associated with a statistically significant [redacted]% reduction in the risk of INV-assessed disease progression or death versus ibrutinib ([redacted]) and statistically significant [redacted]% reduction in the risk of IRC-assessed disease progression or death ([redacted]). Furthermore, late breaking PFS data with a median follow up of 29.6 months, showed a statistically significant 35% reduction in the risk of disease progression or death for zanubrutinib compared with ibrutinib (HR: 0.65; 95% CI: 0.49, 0.86 for both INV- and IRC-assessed PFS).[77]

When assessing outcomes in patients with 17p deletion or TP53 mutations specifically, zanubrutinib was associated with a [redacted]% reduction in the risk of INV-assessed disease progression or death ([redacted]) and statistically significant [redacted]% reduction in the risk of IRC-assessed disease progression or death versus ibrutinib ([redacted]).

To supplement the comparison with ibrutinib, a naïve comparison was conducted to assess the efficacy of zanubrutinib with ibrutinib in patients with untreated CLL. Clinical efficacy for patients with 17p deletion treated with ibrutinib was extracted from Mato et al. (2018) and compared with Cohort 2 (arm C) of SEQUOIA.[89] Mato et al. (2018) was a retrospective study identified within the clinical SLR which presented data on patients who did not meet the inclusion criteria for the RESONATE-2 study (specifically <65 and/or those with 17p deletion). As with the other MAICs, WebPlotDigitizer was used for digitisation, and the IPD from KM method was used for IPD generation and HR estimation.

A formal MAIC was not conducted given that baseline characteristics for patients with a 17p deletion only, to align with the SEQUOIA eligibility criteria of Cohort 2 (arm C), were not published in Mato et al. (2018). Instead, an unstratified Cox regression models was used to estimate HRs for PFS, and OS. Based on this naïve comparison, there was no statistically

significant difference in PFS between zanubrutinib and ibrutinib ([redacted]). However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib ([redacted]).

Both the SEQUOIA and ALPINE trials demonstrate that outcomes are consistent following treatment with zanubrutinib across patients in the previously untreated 'unfit' (Cohort 1 [arm A]) and 'high-risk' (Cohort 2 [arm C]) populations, as well as the R/R population (including patients specifically with 'high-risk' factors). Furthermore, the ELEVATE-RR trial has demonstrated non-inferiority between acalabrutinib and ibrutinib in patients with R/R CLL with high-risk factors. With the MAIC comparing zanubrutinib with acalabrutinib in previously untreated patients (using ELEVATE-TN) and MAIC comparing zanubrutinib with acalabrutinib in patients with 'high-risk' R/R CLL (using ELEVATE-RR – see B.2.9.2.1 Methodology for further details) both demonstrating the non-inferiority of zanubrutinib to acalabrutinib, it follows that zanubrutinib will also be at least non-inferior to ibrutinib within the previously untreated 'high-risk' population.[56]

Considering the evidence versus ibrutinib from ALPINE, the naïve comparison using Mato et al., the consistent outcomes for zanubrutinib across all relevant patient groups and supportive evidence from the ELEVATE-RR trial, coupled with the outcomes of the MAIC comparing SEQUOIA versus ELEVATE-TN – that zanubrutinib is at least non-inferior to acalabrutinib in both previously untreated 'unfit' and 'high-risk' patients – it is clinically plausible to conclude that zanubrutinib will be at least non-inferior to ibrutinib in previously untreated 'high-risk' patients. This conclusion was deemed clinically plausible by UK clinical experts in attendance at an advisory board (03 November 2022) held by the Company.[11]

B.2.9.4.3 Indirect comparison for zanubrutinib versus acalabrutinib in adults with R/R CLL

Two MAICs comparing zanubrutinib with acalabrutinib in patients with R/R CLL were conducted. Following an SLR (Appendix D) and assessment of feasibility, the ELEVATE-RR and ASCEND trial were identified as appropriate trials to inform the efficacy of acalabrutinib in this population of patients.

The ELEVATE-RR trial enrolled only patients with 'high-risk' factors (17p deletion or 11q deletion) and hence, does not reflect the full R/R patient population in the UK. However, given the common comparator arm (ibrutinib) between ALPINE and ELEVATE-RR, it

allowed for an anchored MAIC to be performed. To complement this analysis, an unanchored MAIC was performed using the ASCEND trial. The ASCEND trial population is broader than the ELEVATE-RR trial population, reflecting the full R/R patient population in the UK. However, the given that an anchored MAIC could be performed versus ELEVATE-RR, the ASCEND results are subject to increased uncertainty compared to ELEVATE-RR.

Covariates for matching were selected based on clinical plausibility as indicated by UK clinical experts in attendance at an advisory board (03 November 2022) conducted by the Company, whilst balancing the need to conserve sample size. UK clinical experts did not raise concerns over the ESS and selected covariates for matching in the analyses. After matching, the baseline characteristics in ALPINE were well matched to those reported in ELEVATE-RR and ASCEND.

Both MAIC analyses consistently demonstrated that zanubrutinib is non-inferior to acalabrutinib in patients with R/R CLL. Whilst the HRs for PFS and OS were not statistically significantly different between zanubrutinib and acalabrutinib, zanubrutinib demonstrated a numerical advantage compared to acalabrutinib for PFS across both MAIC analyses, for all models. This is consistent with the MAIC conducted between zanubrutinib and acalabrutinib in patients with previously untreated CLL. The MAICs presented make the best use of the available evidence for zanubrutinib and acalabrutinib and support the conclusion that zanubrutinib is at least non-inferior to acalabrutinib in patients with R/R CLL. UK clinical experts validated this conclusion at an advisory board (03 November 2022) organised by the Company.[11]

B.2a.10 Adverse reactions: previously untreated CLL

The safety results are presented across all patients who received at least one dose of study treatment in SEQUOIA.

B.2a.10.1 Dose exposure

In Cohort 1, the median treatment durations were 5.52 (range: 0.9-7.4) months, 5.59 (range: 0.9-7.4) months, and 26.07 (range 0.5-42.2) months among patients treated with bendamustine, rituximab, and zanubrutinib, respectively. A smaller proportion of patients with dose reductions was observed in the zanubrutinib arm (33 [13.8%]) compared with the BR arm (85 [37.4%]) with AEs attributed as the primary reason for dose reductions in both arms.

In Cohort 2, the overall median treatment duration was 30.00 months for patients treated with zanubrutinib. The percentage of patients with dose reduction was 9.9% and AEs were the primary reason for dose reduction.

B.2a.10.2 Treatment emergent adverse events

A summary of treatment-emergent adverse events (TEAEs) is presented in Table 60. The proportions of patients who experienced TEAEs were comparable between zanubrutinib in Cohort 1 (93.3%) and Cohort 2 (98.2%) and BR (96.0%) in Cohort 1, with the most common AEs presented in Table 61. Discontinuation and death due to TEAEs were less common for patients treated with zanubrutinib compared to patients treated with BR.

In Cohort 1, the incidence of Grade ≥ 3 TEAEs was higher with BR (79.7%) compared with zanubrutinib (52.5%). The most common Grade ≥ 3 TEAEs with zanubrutinib arm were neutropenia (9.2%), hypertension (6.3%), COVID-19 (4.6%), and COVID-19 pneumonia (2.9%). For BR, the most common Grade ≥ 3 TEAEs were neutropenia (41.4%), neutrophil count decreased (10.6%), febrile neutropenia (7.5%), and thrombocytopenia (7.0%). In Cohort 2, 55.0% of patients experienced grade ≥ 3 TEAEs, with neutropenia (10.8%), pneumonia (5.4%), and hypertension and neutrophil count decreased (4.5% each) reported most commonly. The list of Grade ≥ 3 TEAEs reported in ≥2% of patients is presented in Table 62.

Table 60: Summary of treatment-emergent and post-treatment AEs

	Cohort 1		Cohort 2
	BR (N = 227) n (%)	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Treatment-Emergent and Post-Treatment AEs			
Patients with at least one AE	218 (96.0)	224 (93.3)	109 (98.2)
Grade ≥ 3 AEs	181 (79.7)	126 (52.5)	61 (55.0)
Serious AEs	113 (49.8)	88 (36.7)	45 (40.5)
AEs leading to dose modification	159 (70.0)	115 (47.9)	57 (51.4)
AEs leading to treatment discontinuation	31 (13.7)	20 (8.3)	6 (5.4)
AEs leading to death	12 (5.3)	11 (4.6)	3 (2.7)

AE – Adverse event; BR – Bendamustine-rituximab; TEAE – Treatment-emergent adverse event; SAE – Serious adverse event.
Source: SEQUOIA CSR[75]

Table 61: Treatment-emergent and post-treatment adverse events reported in ≥10% of patients in either arm

System Organ Class Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One AE	218 (96.0)	224 (93.3)	109 (98.2)
Infections and infestations	127 (55.9)	149 (62.1)	79 (71.2)
Upper respiratory tract infection	27 (11.9)	41 (17.1)	23 (20.7)
Pneumonia	19 (8.4)	12 (5.0)	13 (11.7)
Gastrointestinal disorders	125 (55.1)	115 (47.9)	64 (57.7)
Diarrhoea	30 (13.2)	33 (13.8)	20 (18.0)
Constipation	43 (18.9)	24 (10.0)	17 (15.3)
Nausea	74 (32.6)	24 (10.0)	18 (16.2)
Vomiting	33 (14.5)	17 (7.1)	8 (7.2)
Skin and subcutaneous tissue disorders	89 (39.2)	106 (44.2)	60 (54.1)
Rash	44 (19.4)	26 (10.8)	16 (14.4)
Musculoskeletal and connective tissue disorders	63 (27.8)	96 (40.0)	54 (48.6)
Arthralgia	20 (8.8)	32 (13.3)	22 (19.8)
Back pain	16 (7.0)	21 (8.8)	16 (14.4)
Respiratory, thoracic and mediastinal disorders	67 (29.5)	86 (35.8)	40 (36.0)
Cough	23 (10.1)	27 (11.3)	14 (12.6)
General disorders and administration site conditions	125 (55.1)	80 (33.3)	33 (29.7)
Fatigue	36 (15.9)	28 (11.7)	10 (9.0)
Pyrexia	60 (26.4)	17 (7.1)	8 (7.2)
Injury, poisoning and procedural complications	69 (30.4)	80 (33.3)	50 (45.0)
Contusion	8 (3.5)	46 (19.2)	22 (19.8)
Infusion related reaction	43 (18.9)	1 (0.4)	0 (0.0)
Nervous system disorders	57 (25.1)	63 (26.3)	32 (28.8)
Headache	17 (7.5)	26 (10.8)	12 (10.8)
Vascular disorders	50 (22.0)	60 (25.0)	27 (24.3)
Hypertension	20 (8.8)	29 (12.1)	10 (9.0)
Blood and lymphatic system disorders	144 (63.4)	52 (21.7)	29 (26.1)
Neutropenia	104 (45.8)	31 (12.9)	13 (11.7)
Anaemia	43 (18.9)	11 (4.6)	6 (5.4)
Thrombocytopenia	31 (13.7)	9 (3.8)	4 (3.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	27 (11.9)	39 (16.3)	30 (27.0)

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System Organ Class Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Basal cell carcinoma	3 (1.3)	11 (4.6)	12 (10.8)
Investigations	65 (28.6)	36 (15.0)	21 (18.9)
Neutrophil count decreased	28 (12.3)	6 (2.5)	7 (6.3)

BR – Bendamustine-rituximab; TEAE – Treatment-emergent adverse event; AE – Adverse event.
Source: SEQUOIA CSR[75]

Table 62: Grade 3 or higher treatment-emergent and post-treatment adverse events reported in ≥2% of patients in either arm

Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One AE of Grade 3 or Higher	181 (79.7)	126 (52.5)	61 (55.0)
Neutropenia	94 (41.4)	22 (9.2)	12 (10.8)
Hypertension	11 (4.8)	15 (6.3)	5 (4.5)
COVID-19	2 (0.9)	11 (4.6)	1 (0.9)
COVID-19 pneumonia	0 (0.0)	7 (2.9)	2 (1.8)
Neutrophil count decreased	24 (10.6)	5 (2.1)	5 (4.5)
Pneumonia	10 (4.4)	4 (1.7)	6 (5.4)
Thrombocytopenia	16 (7.0)	4 (1.7)	1 (0.9)
Febrile neutropenia	17 (7.5)	2 (0.8)	1 (0.9)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Urinary tract infection	6 (2.6)	2 (0.8)	2 (1.8)
Atrial fibrillation	3 (1.3)	1 (0.4)	4 (3.6)
Fall	2 (0.9)	1 (0.4)	3 (2.7)
Hypotension	5 (2.2)	1 (0.4)	2 (1.8)
Infusion related reaction	6 (2.6)	0 (0.0)	0 (0.0)
Leukopenia	5 (2.2)	0 (0.0)	0 (0.0)
Pyrexia	8 (3.5)	0 (0.0)	1 (0.9)
Rash	6 (2.6)	0 (0.0)	0 (0.0)

BR – Bendamustine-rituximab; TEAE – Treatment-emergent adverse event; AE – Adverse event. Source: SEQUOIA CSR[75]

B.2a.10.3 Serious AEs

In the SEQUOIA trial, a serious AE (SAE) was defined as any untoward medical occurrence that, at any dose, which resulted in death, was life-threatening, required hospitalisation or

prolongation of existing hospitalisation, resulted in disability/incapacity or was a congenital anomaly/birth defect. An event that did not meet these criteria was considered an SAE by the investigator when, based upon appropriate medical judgement, the event may have jeopardised the patient or may have required intervention to prevent one of the other outcomes listed above.

In Cohort 1, SAEs were reported in 36.7% and 49.8% of patients in the zanubrutinib and BR arms, respectively. The most common SAEs were COVID-19 (3.3%) and COVID-19 pneumonia (2.9%) in the zanubrutinib arm and pyrexia (7.5%) and febrile neutropenia (4.8%) in the BR arm.

In Cohort 2, SAEs were reported in 40.5% of patients, with pneumonia (5.4%), fall, and atrial fibrillation (2.7%) reported most commonly.

B.2a.10.4 Deaths

As of the data cut-off of 07 March 2022, [redacted] deaths had occurred in Cohort 1; [redacted] in the zanubrutinib arm and [redacted] in the BR arm after a median follow-up of 36.1 months and 35.4 months, respectively. AEs were the most common cause of death in both the BR and zanubrutinib arms, accounting for [redacted] and [redacted] deaths, respectively. The most common AEs leading to death were COVID-19, pneumonia, diarrhoea, and pneumonia aspiration [redacted] in the BR arm and COVID-19 [redacted] and COVID-19 pneumonia [redacted] in the zanubrutinib arm.

As per the data-cut off on 07 May 2021, only [redacted] deaths were reported in Cohort 2 at a median follow-up time of 30.4 months. Progressive disease and AEs were the most common cause of death in Cohort 2, accounting for [redacted] and [redacted] deaths, respectively. No patients died due to COVID-19 or COVID-19 pneumonia in Cohort 2.

B.2a.10.5 Safety overview

Zanubrutinib is tolerable and safe in the treatment of patients with untreated CLL with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies.[22,90] Across Cohorts 1 and 2, the incidences of AEs were generally comparable between the zanubrutinib and BR arms though fewer patients in the zanubrutinib arms experienced Grade ≥ 3 TEAEs or SAEs. Aside from COVID-19 events stemming from the global pandemic, no additional new AEs were identified in the safety profile of zanubrutinib.

Cardiac AE incidence, such as atrial fibrillation/flutter, can be a substantial limiting factor of BTK inhibitor treatment. An increased rate of atrial fibrillation was reported with ibrutinib versus CIT treatment in randomised studies.[57,58] The SEQUOIA trial reported low atrial fibrillation rates for zanubrutinib, occurring in 8 (3.3%) of patients in Cohort 1 and 5 (4.5%) of patients in Cohort 2, these rates were similar to those reported in the BR arm (2.6%). No sudden deaths were reported in either study arm.

B.2b.10 Adverse reactions: R/R CLL

The safety results are presented across all patients who received at least one dose of study treatment in ALPINE.

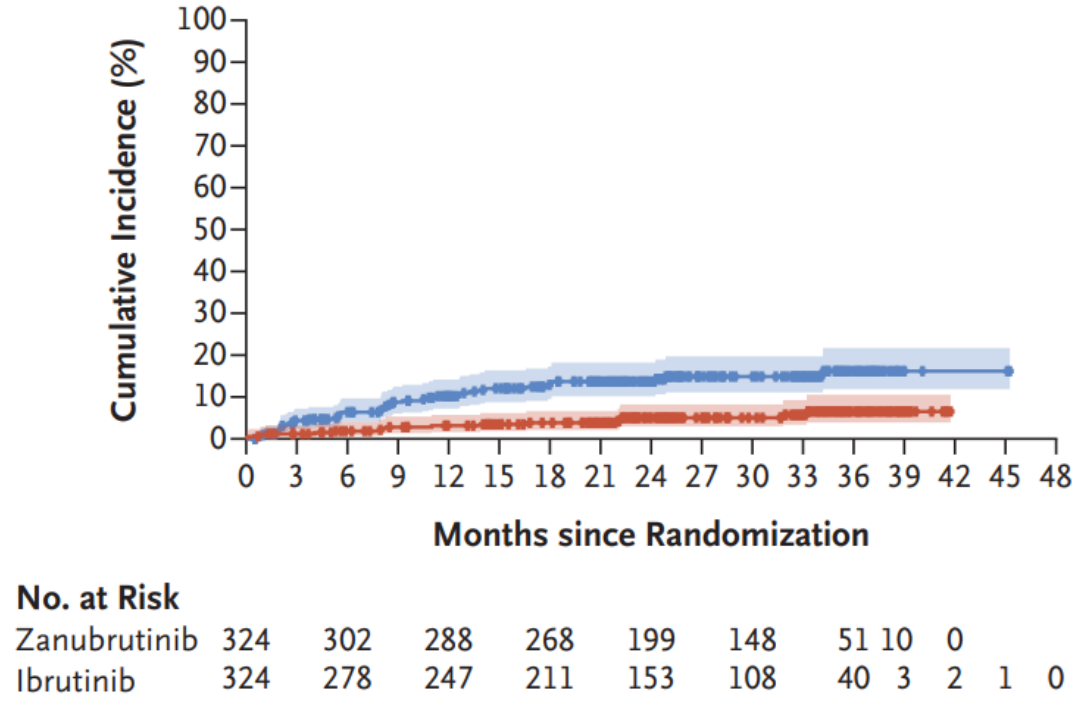
B.2b.10.1 Dose exposure

The median treatment duration was [redacted] (range: [redacted]) months in the zanubrutinib arm and [redacted] (range: [redacted]) months in the ibrutinib arm. A smaller proportion of patients with dose reduction or dose interruption was observed in the zanubrutinib arm ([redacted]) than in the ibrutinib arm ([redacted]) with AEs attributed as the primary reason for dose reductions or dose interruption in both arms.

B.2b.10.2 Treatment emergent adverse events

A summary of the TEAEs is presented in Table 63. The proportion of patients who experienced TEAEs were comparable between zanubrutinib [redacted] and ibrutinib [redacted] with the most common AEs presented in Table 64. Of note, zanubrutinib had lower cardiac AEs than ibrutinib and of particular note, a statistically significant reduction in the incidence of atrial fibrillation or flutter [redacted], a key secondary endpoint. Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, demonstrated that the reduction in the incidence of atrial fibrillation or flutter [redacted] was maintained, as demonstrated in Figure 43.[77] Discontinuation and death due to TEAEs were less common for patients treated with zanubrutinib compared to patients treated with ibrutinib.

Figure 43: Time to the occurrence of atrial fibrillation or flutter in ALPINE



Source: Brown et al. (2022)[91]. Zanubrutinib – red line; ibrutinib – blue line.

The incidence of Grade ≥ 3 TEAEs was higher in the ibrutinib arm [redacted] compared with the zanubrutinib arm [redacted] The most common Grade ≥ 3 TEAEs with zanubrutinib arm were neutropenia [redacted] hypertension [redacted] and COVID-19 pneumonia [redacted] For ibrutinib, the most common Grade ≥ 3 TEAEs were neutropenia [redacted] hypertension [redacted] and pneumonia [redacted]. The list of Grade ≥ 3 TEAEs reported in ≥1% of patients is presented in Table 65. Late breaking data from DCO 08 August 2022, with a median follow up of 29.6 months, demonstrated consistency with the safety outcomes presented within the submission.[77]

Table 63: Summary of treatment-emergent and post-treatment AEs

	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Treatment-Emergent and Post-Treatment AEs		
Patients with at least one AE	[redacted]	[redacted]
Grade ≥ 3 AEs	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]
AEs leading to dose modification	[redacted]	[redacted]

	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
AEs leading to treatment discontinuation	[redacted]	[redacted]
Patients with at least one AE	[redacted]	[redacted]

TEAE – Treatment-emergent adverse event; AE – Adverse event.
Source: ALPINE CSR[76]

Table 64: Treatment-emergent and post-treatment adverse events reported in ≥5% of patients in either arm

System organ class preferred term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders		
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders		
Atrial fibrillation	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
General disorders and administration site conditions		
Fatigue	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Infections and infestations		
Upper respiratory tract infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Injury, poisoning and procedural complications		
Contusion	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Investigations		
Neutrophil count decreased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]

System organ class preferred term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Metabolism and nutrition disorders		
Hyperuricaemia	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders		
Arthralgia	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Nervous system disorders		
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		
Cough	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Skin and subcutaneous tissue disorders		
Rash	[redacted]	[redacted]
Petechiae	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]

TEAE – Treatment-emergent adverse event; AE – Adverse event.
Source: ALPINE CSR[76]

Table 65: Grade 3 or higher treatment-emergent adverse events by system organ class and preferred term ≥1% in either arm (safety analysis set)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One Grade 3 or Higher TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders		
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cardiac disorders		
Atrial fibrillation	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	[redacted]	[redacted]
General disorders and administration site conditions		

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Pyrexia	[redacted]	[redacted]
Infections and infestations		
Pneumonia	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Investigations		
Neutrophil count decreased	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Metabolism and nutrition disorders		
Diabetes mellitus	[redacted]	[redacted]
Nervous system disorders		
Syncope	[redacted]	[redacted]
Renal and urinary disorders		
Acute kidney injury	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]

TEAE – Treatment-emergent adverse event; AE – Adverse event.
Source: ALPINE CSR[76]

B.2b.10.3 Serious AEs

In the trial, a SAE was defined as any untoward medical occurrence that, at any dose, which resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in disability/incapacity or was a congenital anomaly/birth defect. An event that did not meet these criteria was considered an SAE by the investigator when, based upon appropriate medical judgement, the event may have jeopardised the patient or may have required intervention to prevent one of the other outcomes listed above.

SAEs were more common in the ibrutinib arm than the zanubrutinib arm, with [redacted]% and [redacted]% of patients experiencing a SAE, respectively. The most common SAEs were COVID-

19 pneumonia [redacted] COVID-19 and COVID-19 [redacted] COVID-19 in the zanubrutinib arm and pneumonia [redacted] and COVID-19 pneumonia [redacted] in the ibrutinib arm.

B.2b.10.4 Deaths

As of the data cut-off of 01 December 2021, [redacted] deaths had occurred; [redacted] in the zanubrutinib arm and [redacted] in the ibrutinib arm after a median follow up of 24.9 and 24.6 months, respectively. AEs were the primary cause of death in both the zanubrutinib and ibrutinib arms, accounting for [redacted] and [redacted] deaths, respectively. The most common AEs leading to death were COVID-19 [redacted], COVID-19 pneumonia [redacted] and pneumonia [redacted] in the zanubrutinib arm and COVID-19 pneumonia [redacted], pneumonia [redacted] and COVID-19 [redacted] in the ibrutinib arm.

In the ibrutinib arm[redacted] died due to a cardiac AE, all of which occurred ≤ 30 days after the last dose of study drug. No patients in the zanubrutinib arm died due to a cardiac AE.

B.2b.10.5 Safety overview

Zanubrutinib is tolerable and safe in the treatment of patients with R/R CLL, with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies..[92,93] The rate of atrial fibrillation was statistically significantly lower in the zanubrutinib arm [redacted] compared to ibrutinib [redacted]. The rate difference between the arms was [redacted], showing a statistically significant difference, which was consistent at a later datacut.[91] There were no deaths due to cardiac disorders with zanubrutinib whereas [redacted] patients treated with ibrutinib died due to a cardiac AE, all of which occurred ≤ 30 days after the last dose of study drug. As a next-generation BTKi, these results support the hypothesis that reduced inhibition of off-target kinases with zanubrutinib might avoid increased risk of cardiac AEs observed with ibrutinib and offer a potential improvement on the safety profile.

Aside from COVID-19 events stemming from the global pandemic, no additional new AE were identified in the safety profile of zanubrutinib.

B.2.11 Ongoing studies

The SEQUOIA study is ongoing and expected to complete in 2024. Subsequent data cuts are expected to provide additional OS and safety data in 2023.[94]

The ALPINE study is ongoing and expected to complete in 2023. No additional data cuts from ALPINE are anticipated during the NICE appraisal.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Efficacy in previously untreated CLL

Comparison with BR

In the SEQUOIA trial, the primary endpoint was met with zanubrutinib demonstrating superior IRC-assessed PFS versus BR in previously untreated patients without a 17p deletion. When compared to treatment with BR, treatment with zanubrutinib was associated with a statistically significant 58% reduction in the risk of disease progression or death (HR:0.42; 95% CI: 0.28, 0.63; p<0.0001). The improvement in PFS was consistent across several high-risk subgroups such as unmutated IGHV, bulky disease and 13q deletion and was similarly observed in the INV-assessed PFS endpoint.

The SEQUOIA trial also met a number of its secondary endpoints, demonstrating a statistically significant improvement in ORR and DOR as determined by both IRC and INV assessment. Furthermore, when compared to treatment with BR, zanubrutinib was associated with a 7% reduction in the risk of death (HR:0.93; 95% CI: 0.52, 1.67; p=0.41), with further stratification expected at future data cuts.

Cohort 2 of SEQUOIA is among the largest bodies of prospective evidence collected specifically for patients with a 17p deletion and demonstrated consistent outcomes following treatment with zanubrutinib in patients with or without a 17p deletion. PFS, OS, ORR and DOR were all comparable across patients treated with zanubrutinib in Cohort 1 and Cohort 2, demonstrating the survival benefit and that both depth and duration of response are consistent. Of note, ORR determined by IRC-assessment in Cohort 2 was 90.0% (95% CI: 82.8, 94.9), with 88.2% (95 CI: 80.6, 93.6) having a best overall response of PR or higher.

Comparison with acalabrutinib

A MAIC was conducted which demonstrated that zanubrutinib is at least non-inferior to acalabrutinib (PFS HR: 0.89; 95% CI, 0.50, 1.59; OS HR: 1.05; 95% CI, 0.44, 2.48) in previously untreated adults with CLL who are unsuitable for FCR and BR therapy, both **with and without 17p deletion**. Feedback received from an advisory board conducted by the Company (03 November 2022) agreed that the HRs were **clinically plausible** for PFS though noted that the CIs were wide due to immature data for long-term outcomes from SEQUOIA. In particular, the experts noted that the low number of deaths in SEQUOIA leads to high uncertainty in the relative OS estimates. Furthermore, the experts also noted that the unadjusted and adjusted KMs for PFS and OS were similar for zanubrutinib and acalabrutinib, supporting the non-inferiority of zanubrutinib to acalabrutinib.[11]

The MAIC was conducted using pooled data for zanubrutinib from Cohort 1 (arm A) and Cohort 2 (arm C) of the SEQUOIA trial to match the available evidence from ELEVATE-TN. Following an SLR and assessment of feasibility, no publications for acalabrutinib were identified which reported population characteristics and outcomes specifically for previously untreated patients with or without 17p deletion. As such, there was insufficient data to conduct an ITC separately for these populations. However, the vast majority (93.3%) of the population informing the MAIC did not have 'high-risk' factors, i.e., 17p deletion or TP53 mutation.

Whilst there is a paucity of evidence specifically reported in patients with a 17p deletion, the results are reflective of the relative efficacy of zanubrutinib versus acalabrutinib across both the previously untreated 'unfit' and 'high-risk' populations, with both the ELEVATE-TN or SEQUOIA trials reporting consistent outcomes for patients with and without 17p deletion.

In TA429 and TA689, NICE provided a recommendation for acalabrutinib and ibrutinib, respectively, in previously untreated adults with CLL who have a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable based on data presented in previously treated patients. Data from RESONATE and ASCEND were used as a proxy to support the reimbursement decisions in this population. Two MAICs have been conducted comparing outcomes with zanubrutinib versus acalabrutinib in patients with R/R CLL as described in Section B.2.9.2 Indirect comparison for zanubrutinib versus acalabrutinib using ELEVATE-RR in R/R CLL and B.2.9.3 Indirect comparison for zanubrutinib versus acalabrutinib using ASCEND. These analyses demonstrated that zanubrutinib is at least non-inferior to

acalabrutinib in patients with R/R CLL. As the MAICs conducted using ELEVATE-RR and ASCEND contained a high proportion of patients with a 17p deletion or TP53 mutation (~40% each), these analyses are deemed highly relevant as a proxy for previously untreated patients with 17p deletion or TP53 mutation.

The MAICs presented make the best use of the available evidence for zanubrutinib and acalabrutinib**.** The MAIC conducted in the previously untreated population, coupled with MAICs conducted in the R/R population, support the conclusion that zanubrutinib is at least non-inferior to acalabrutinib across both the previously untreated 'unfit' and 'high-risk' populations.

Comparison with ibrutinib

Ibrutinib is only approved by NICE in previously untreated 'high-risk' patients with CLL.[88] As there is a paucity of evidence specifically reported in patients with a 17p deletion or TP53 mutation, there was insufficient data to conduct a MAIC versus ibrutinib in the previously untreated 'high-risk' population, with both of the key phase 3 clinical trials for ibrutinib (RESONATE-2 and ALLIANCE) only recruiting a minority of patients with these 'high-risk' factors. This conclusion was supported by UK experts in attendance at an advisory board (03 November 2022) held by the Company.[11] With data in patients with R/R CLL having been previously accepted by NICE as a proxy to support reimbursement decisions in this population (previously untreated 'high-risk'), head-to-head results comparing zanubrutinib with ibrutinib from the ALPINE trial were deemed highly relevant in this population.[78,88] Zanubrutinib is associated with a statistically significant 45% reduction in the risk of INV-assessed disease progression or death versus ibrutinib ([redacted]) (DCO 01 December 2021). Furthermore, when assessing outcomes in patients with 17p deletion or TP53 mutations specifically, zanubrutinib was associated with a [redacted]% reduction in the risk of INV-assessed disease progression or death (HR:0.53, 95% CI: 0.27-1.01) and statistically significant [redacted]% reduction in the risk of IRC-assessed disease progression or death versus ibrutinib ([redacted]) (DCO 01 December 2021). In addition, a naïve comparison using Mato et al. (2018) in untreated patients with 17p deletion indicated no statistically significant difference in PFS between zanubrutinib and ibrutinib ([redacted]).[89]

As such, it is clinically plausible to conclude that zanubrutinib will be at least non-inferior to ibrutinib in previously untreated 'high-risk' patients. This conclusion was deemed clinically

plausible by UK clinical experts in attendance at an advisory (03 November 2022) held by the Company.[11]

B.2.12.2 Efficacy in R/R CLL

Comparison with ibrutinib

The ALPINE trial met its primary endpoint, with zanubrutinib demonstrating a statistically significant improvement in ORR determined by INV-assessment. ORR determined by INV-assessment was higher for patients in the zanubrutinib arm (79.5%) compared with the ibrutinib arm (71.1%) representing a response ratio of 1.12 (95% CI: 1.02, 1.22; p=0.0133). The improvement in ORR was consistent across several high-risk subgroups, such as unmutated IGHV, bulky disease and 13q deletion and was similarly observed in the ICR-assessed ORR endpoint.

Clinical superiority of zanubrutinib over ibrutinib was supported by consistently better outcomes in secondary endpoints. At the 2021 data cut off, when compared to treatment with ibrutinib, treatment with zanubrutinib was associated with a statistically significant 45% reduction in the risk of INV-assessed disease progression or death (HR: 0.55; 95% CI: 0.39 to 0.76); p=0.0004). The PFS benefit of zanubrutinib was confirmed in recent more mature late breaking data which, after a median follow-up of approximately 30 months, demonstrated that zanubrutinib was associated with a statistically significant 31% reduction in both INV-assessed (HR: 0.69; 95% CI 0.49 – 0.86) and IRC-assessed (HR: 0.69; 95% CI 0.49 – 0.86) progression or death compared to ibrutinib. This makes zanubrutinib the first BTKi to demonstrate superiority against an alternative BTKi on a clinically meaningful endpoint, namely PFS.

Furthermore, fewer patients discontinued zanubrutinib - the proportion of patients with treatment failure in the zanubrutinib arm was statistically significantly lower (19.3%) than in the ibrutinib arm (33.2%) at a median follow-up of 25.1 months in both arms, resulting in a 50% reduction in the risk of treatment failure (HR: 0.50; 95% CI: 0.36, 0.68; p<0.0001). This demonstrates the improved tolerability of zanubrutinib over ibrutinib. In addition, statistically significantly lower rates in the key secondary endpoint of incidence of atrial fibrillation or flutter were reported in patients in the zanubrutinib arm (4.6%) compared to ibrutinib arm (12%), highlighting the improved cardiac safety profile of zanubrutinib.

Comparison with acalabrutinib

The ELEVATE-RR and ASCEND trials were identified as appropriate trials to inform the relative efficacy of zanubrutinib versus acalabrutinib in patients with R/R CLL.

A MAIC was conducted using ELEVATE-RR which demonstrated that zanubrutinib is non-inferior to acalabrutinib (IRC-assessed PFS HR: 0.62; 95% CI: 0.26, 1.47, INV-assessed PFS HR: 0.63; 95% CI: 0.28, 1.42, OS HR: 0.69; 95% CI: 0.28, 1.72) in patients with R/R CLL who had received at least one systemic therapy. During an advisory board conducted by the Company (03 November 2022), experts did not raise concerns with the clinical plausibility of the HRs for PFS and OS and supported the conclusion of non-inferiority for zanubrutinib and acalabrutinib.[11]

Furthermore, a second MAIC was conducted to supplement the ELEVATE-RR MAIC, using ASCEND which also confirmed that zanubrutinib is non-inferior to acalabrutinib (PFS HR: 0.81; 95% CI: 0.47, 1.43, OS HR: 1.07; 95% CI: 0.55, 2.07). There was little change in the pre-matching and post-matching KMs for zanubrutinib, which suggests that the populations in ALPINE and ASCEND were well-balanced, and the results are consistent with the findings from the ELEVATE-RR MAIC. Due to the common ibrutinib comparator arm between ALPINE and ELEVATE-RR, an anchored MAIC could be performed, which reduces the uncertainty in the analyses compared to the ASCEND MAIC.

Overall, the MAICs presented make the best use of the available evidence for zanubrutinib and acalabrutinib in patients with R/R CLL**.** The MAICs conducted using data from both ELEVATE-RR and ASCEND support the conclusion that zanubrutinib is at least non-inferior to acalabrutinib in the patients with R/R CLL and are consistent with the conclusions drawn about the relative efficacy between zanubrutinib and acalabrutinib in patients with previously untreated CLL (See Section B.2.9 Indirect and mixed treatment comparisons for further details).

B.2.12.3 Safety

Zanubrutinib is tolerable and safe in the treatment of patients with previously untreated and R/R CLL with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies.[22,90]

Across Cohorts 1 and 2 of SEQUOIA, the incidences of AEs were generally comparable between the zanubrutinib and BR arms though fewer patients in the zanubrutinib arms

experienced Grade ≥ 3 TEAEs or SAEs. In addition, the proportion of patients who experienced AEs in ALPINE were comparable between the zanubrutinib and ibrutinib arms, though SAEs were more common in the ibrutinib arm than in the zanubrutinib arm. Aside from COVID-19 events stemming from the global pandemic, no additional new AEs were identified in the safety profile of zanubrutinib in either SEQUOIA or ALPINE.

The results of the SEQUOIA and ALPINE trials confirmed that zanubrutinib is a next-generation BTKi with an improved cardiac safety profile. The SEQUOIA trial reported low atrial fibrillation rates for zanubrutinib, occurring in 8 (3.3%) patients in Cohort 1 and 5 (4.5%) patients in Cohort 2, these rates were similar to those reported in the BR arm (2.6%). In comparison, an increased rate of atrial fibrillation was reported with ibrutinib versus CIT treatment in randomised studies.[57,58] In the ALPINE trial, the rate of atrial fibrillation or flutter a key secondary endpoint, was statistically significantly lower in the zanubrutinib arm (4.6%) compared to ibrutinib (12.0%). No sudden deaths with zanubrutinib were reported in either trial. In ALPINE there were no deaths due to cardiac disorders with zanubrutinib whereas five patients treated with ibrutinib died due to a cardiac AE, all of which occurred ≤ 30 days after the last dose of study drug.

The safety profile of zanubrutinib in CLL is consistent with the safety profile in other B-cell malignancies, where zanubrutinib was demonstrated to be well-tolerated.[68,90] As a next-generation BTKi with less off-target effects, these results support the hypothesis that reduced inhibition of off-target kinases with zanubrutinib might avoid increased risk of cardiac AEs observed with ibrutinib.

B.3a Cost-effectiveness: previously untreated CLL

B.3a.1 Published cost-effectiveness studies

An SLR was conducted to identify studies reporting the cost-effectiveness, HRQoL and cost and resource use of patients with previously untreated or R/R CLL (Section B.3b.2 Economic analysis). Full details of the process and methods used to identify and select the economic evidence relevant to the technology being evaluated are presented in Appendices G-H.

The SLR identified three cost-effectiveness studies from a UK perspective and two NICE appraisals for patients with either previously untreated CLL or patients with R/R CLL. A summary of these studies is provided in Table 66; only those studies which report results for the comparators of interest (acalabrutinib and ibrutinib) and a UK perspective were extracted.

Table 66: Published cost-effectiveness studies identified through the SLR

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Munir (2020) (conference abstract)[95]	2020	3-state semi-Markov model was developed, consisting of mutually exclusive health states: PFS, PD, and death	Patients with previously untreated CLL who are considered ineligible for fludarabine-based treatment Age: NR	QALYs gained: Acalabrutinib: 7.48 Chlorambucil-obinutuzumab: 6.34 Difference: 1.14	Initial treatment costs (£): Acalabrutinib: 368,300 Chlorambucil-obinutuzumab: 26,757 Difference: +341,543	£30,701
Sinha (2018) (article)[96]	2018	3-state Markov model was developed consisting of mutually exclusive health states: PFS, PD, and death.	Previously untreated patients (18 years or older) with CLL with comorbidities Age: >18 years	QALYs gained: G-Clb: 6.83 IB: 8.32 Incremental: 1.49	Total costs (£) G-Clb: 208,154 IB: 320,988 Incremental: 112,835	£75,648
Hassan (2017) (abstract)[97]	2017	3-state PartSA model was used to extrapolate PFS and OS. Model health states were PFS, PD and death.	Patients with R/R CLL Age: NR	Incremental QALYs: Ibrutinib vs Ofatumumab: 2.48 Ibrutinib vs PC: 3.07 Ibrutinib vs IR : 1.82 Ibrutinib vs BR: 3.36	NR	Ibrutinib vs Ofatumumab: £53,245 Ibrutinib vs PC: £52,787 Ibrutinib vs IR : £53,644 Ibrutinib vs BR: £49,023

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA689[78]	2020	Untreated: 3-state semi-Markov model (PF, PD, Death) R/R: 3-state PartSA (PFS, PD and death)	Adult patients with untreated and treated CLL Mean age: untreated – 70 years; treated – 67 years	Redacted	Redacted	Redacted
NICE TA429[16]	2017	3-state PartSA (PFS, PD and death)	Adult patients with CLL who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy Mean age: 71 years	Incremental QALY Ibrutinib vs Ofatumumab: 2.65 Ibrutinib vs PC: 3.29 Ibrutinib vs IR : 1.93 Ibrutinib vs BR: 3.61	Incremental costs Ibrutinib vs Ofatumumab: £120,487 Ibrutinib vs PC: £149,589 Ibrutinib vs IR : £86,718 Ibrutinib vs BR: £151,595	Ibrutinib vs Ofatumumab: £34,345 Ibrutinib vs PC: £33,843 Ibrutinib vs IR : £33.203 Ibrutinib vs BR: £30,828

BR – bendamustine-rituximab; CLL - chronic lymphocytic leukaemia; ICER – Incremental cost-effectiveness ratio; IR – idelalsib-rituximab; G-Clb – obinutuzumab-chlorambucil; NR – not reported; OS – overall survival; PartSA – Partitioned survival analysis; PC – Physician's choice; PD – progressed disease; PFS – progression-free survival; QALYs – Quality-adjusted life years; SLR – Systematic literature review; R/R – relapsed/refractory; vs – versus.

B.3a.2 Economic analysis

The SLR did not identify any previous economic evaluations of zanubrutinib in patients with previously untreated CLL.

As discussed in B.2.9 Indirect and mixed treatment comparisons , a MAIC was conducted which demonstrated that zanubrutinib is at least non-inferior to acalabrutinib in patients with previously untreated CLL who are unsuitable for FCR and BR therapy, irrespective of 17p deletion and/or TP53 mutation. In addition, the results of two additional MAICs conducted in the R/R setting (which has previously been accepted by NICE as a proxy for 'high-risk' previously untreated patients) and clinical expert opinion support the conclusion that zanubrutinib is at least non-inferior to acalabrutinib across both the previously untreated 'unfit' and 'high-risk' populations.[4,11,16]

Furthermore, it is clinically plausible to conclude that zanubrutinib will be at least non-inferior to ibrutinib in patients with previously untreated 'high-risk' CLL, with this conclusion supported by both head-to-head data from ALPINE in patients with R/R CLL (which has previously been accepted by NICE as a proxy for 'high-risk' patients) and clinical expert opinion (see Section B.2.9 Indirect and mixed treatment comparisons).[4,11,16]

To reflect these findings, a cost-minimisation analysis (CMA) was developed in Microsoft® Excel to estimate the incremental costs of zanubrutinib versus acalabrutinib ('unfit' and 'high-risk' populations) and versus ibrutinib ('high-risk' population).

The SLR identified one economic evaluation utilising a CMA approach. In TA689, a semi-Markov model structure was used to compare acalabrutinib versus ibrutinib within a CMA.[4] To align with the past precedence of this CMA being accepted by NICE, a semi-Markov structure was utilised to compare zanubrutinib with acalabrutinib in both 'unfit' and 'high-risk' patients and ibrutinib in 'high-risk' patients only. The choice of model structure was validated by clinical and economic experts in attendance at an advisory board (03 November 2022) held by the Company, with the model structure deemed suitable for the decision problem.[11]

Key characteristics of the CMA are presented in Table 67 and compared against the characteristics of previous economic evaluations submitted to NICE for BTKi treatments in patients with previously untreated CLL.

Table 67: Features of the economic analysis

Factor	Previous evaluations for BTKis		Current evaluation	
	NICE TA429[16]	NICE TA689[4]	Chosen values	Justification
Intervention	Ibrutinib	Acalabrutinib	Zanubrutinib	In line with the final NICE scope
Comparators	Alemtuzumab with or without corticosteroids; idelalisib-rituximab; BSC	Chlorambucil-obinutuzumab ('unfit'); ibrutinib ('high-risk')	Acalabrutinib ('unfit' and 'high-risk'); ibrutinib ('high-risk')	In line with the final scope (please refer to Section B.1.1 Decision problem, description of the technology and clinical care pathway for additional rationale)
Modelling approach	PSM; cost-utility	3-health state semi-Markov; cost-utility (versus chlorambucil-obinutuzumab) and cost-minimisation (versus ibrutinib)	3-health state semi-Markov; cost-minimisation	This approach has been applied in several previous HTA submissions for anti-cancer treatments in CLL (TA689, TA487, TA359, TA343)[4,98–100] Allows flexibility to model PPS based on external published data and avoids dependency on immature OS data
Approval population	Adults with untreated CLL associated with 17p deletion or TP53 mutation for whom CIT is not suitable	Previously untreated CLL who are ineligible for FCR and BR; Previously untreated CLL with 17p del or TP53 mutation in whom CIT is unsuitable	Patients with previously untreated CLL without 17p deletion or TP53 mutation for whom CIT is unsuitable; Patients with previously untreated CLL with 17p deletion or TP53 mutation for whom CIT is unsuitable	Aligned with the anticipated licence for zanubrutinib (please refer to Section B.1.1 Decision problem for additional rationale)
Perspective	UK NHS and PPS	UK NHS and PPS	UK NHS and PPS	Consistent with NICE reference case[101]
Time horizon	20 years	30 years	Lifetime (30 years)	Lifetime horizon (30 years) is required to capture all differences in treatment arms in the economic model

Factor	Previous evaluations for BTKis		Current evaluation	
	NICE TA429[16]	NICE TA689[4]	Chosen values	Justification
Cycle length	4-week	4-week	4-week	Consistent with design of SEQUOIA which uses a period of 4 weeks for drug administration cycles
Half-cycle correction	Yes	Yes	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and end of each cycle
Source for clinical efficacy: progression-free	RESONATE; Study OMB114242; CLL2M GCLLSG; HELIOS; Study 119; Study 116	ELEVATE-TN	SEQUOIA	TTP and PrePS were derived from the SEQUOIA trial for zanubrutinib
Source for clinical efficacy: post-progression	RESONATE	RESONATE; MURANO	MURANO	OS from SEQUOIA was deemed too immature to provide robust parametric modelling estimates. As such, PPS from external published data sources were leveraged and aligned to the anticipated subsequent treatments prescribed as per the treatment pathway in the UK. Patients progressing on a BTKi, would typically be ineligible for a BTKi in the second line and would receive treatment with a venetoclax-based regimen
Safety	RESONATE	ELEVATE-TN, RESONATE-2	SEQUOIA; ELEVATE-TN, ALLIANCE, RESONATE-2	Safety data from key clinical trials for treatment arms

Factor	Previous evaluations for BTKis		Current evaluation	
	NICE TA429[16]	NICE TA689[4]	Chosen values	Justification
Utilities	RESONATE; Beusterien 2010[102]	Ara & Brazier 2010[103]; Holzner 2004[104]	Base-case: N/A Scenario: Ara & Brazier 2010[103] and Holzner 2004[104]	A cost-minimisation approach was used. A cost-utility analysis was provided as a scenario utilising data from Ara & Brazier 2010[103] and Holzner 2004[104]
Costs	Treatment acquisition and administration Disease management End-of-life Management of Grade 3 or above adverse events Subsequent therapies	Treatment acquisition and administration Disease management End-of-life Management of Grade 3 or above adverse events Subsequent therapies	Treatment acquisition and administration Disease management End-of-life Management of Grade 3 or above adverse events Subsequent therapies	Consistent with NICE reference case[101]
Outcomes	Total (aggregated and disaggregated) costs, LYs and QALYs Incremental costs, LYs and QALYs ICER	Total (aggregated and disaggregated) costs, LYs and QALYs Incremental costs, LYs and QALYs ICER	Base-case: Total (aggregated and disaggregated) costs and incremental costs Scenario analyses: LYs, QALYs, incremental LYs and QALYs and ICER	Consistent with the final scope for this appraisal and the NICE reference case[101]
Uncertainty	OWSA Scenario analysis Probabilistic sensitivity analysis	OWSA Scenario analysis Probabilistic sensitivity analysis	OWSA Scenario analysis Probabilistic sensitivity analysis	Consistent with the NICE reference case[101]

BR – Bendamustine-rituximab; BSC – Best supportive care; BTKi – Burton tyrosine kinase inhibitor; CIT – Chemo-immunotherapy; CLL – Chronic lymphocytic leukaemia; FCR – Fludarabine-cyclophosphamide-rituximab; HTA – Health technology assessment; ICER – incremental cost-effectiveness ratio; LY – Life year; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; OS – Overall survival; OWSA – One-way sensitivity analysis; PPS – Post-progression survival; PrePS – Pre-progression survival; PSM – Partitioned survival model; QALY – Quality-adjusted life year; TTP – Time-to-progression; UK – United Kingdom.

B.3a.2.1 Patient population

The CMA evaluates the cost-difference of treatment with zanubrutinib compared with acalabrutinib in previously untreated 'unfit' patients and compared with both acalabrutinib and ibrutinib in previously untreated 'high-risk' patients. The baseline characteristics for the modelled population are presented in Table 68.

Table 68: Baseline characteristics for modelled population

Characteristics	Mean (SE)	Source
Age (years)	[redacted]	SEQUOIA CSR Table 14.1.2.1.3
Weight (kg)	[redacted]	SEQUOIA CSR Table 14.1.2.1.3
BSA (m^2)	1.92 (0.20)	Calculation
Proportion female	[redacted]	SEQUOIA CSR Table 14.1.2.1.3

BSA – Body surface area; CSR – Clinical study report; N/A – Not applicable; SE – Standard error.

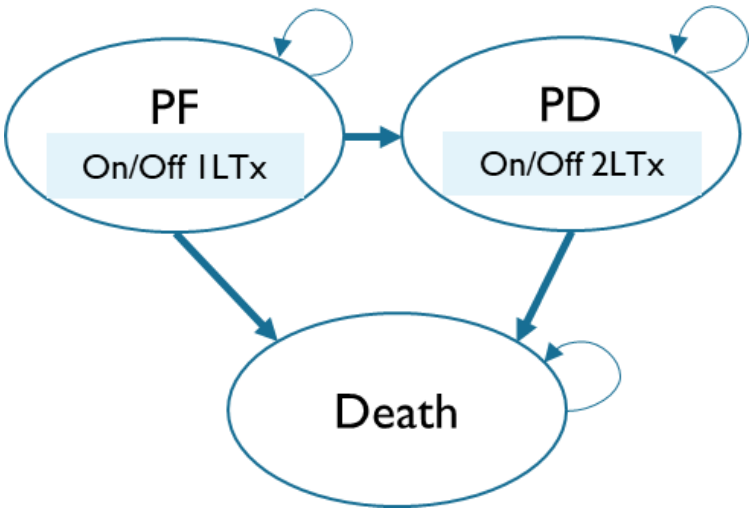
B.3a.2.2 Model structure

The CMA was performed within a full cost-effectiveness model framework. As illustrated in Figure 44, a 3-health state semi-Markov model was developed. The model utilises three mutually exclusive health states to model patients' survival outcomes over the time horizon: progression-free (PF), progressed disease (PD), and death. All patients initiate in the PF health state and can transition to the PD health state upon disease progression. Patients progressing to the PD state in each cycle are tracked using second-line PFS data to allow more complete modelling of subsequent treatments, whilst maintaining the relationship between PFS and OS.

A four-week (28 day) cycle length was used to accommodate the administration schedule of treatment regimens, whilst allowing sufficient granularity to accurately capture differences in cost and health effects between cycles. A lifetime (30 year) time horizon allowed long-term treatment costs to be captured.

Total costs of treatments were estimated by combining the proportion of patients in each health state over time with the costs assigned to the respective state.

Figure 44: Health state structure used in the economic model



PD – Progressed disease; PF – Progression-free; 1LTx – First-line treatment; 2LTx – Second-line treatment.

B.3a.2.3 Health states

The model structure includes the following health states:

- **PF**: All patients initiate in the PF state and receive first-line treatment until either discontinuation, progression or death. After the first cycle of treatment, patients can discontinue treatment whilst remaining in the PF state until either progression or death.

- **PD**: The PD state captures patients who have progressed on their first-line therapy and moved on to a subsequent line of treatment, with patients occupying this health state until death. After the first cycle of secondary treatment, patients can discontinue treatment whilst remaining in the PD state until death.

- **Death**: The death state is an absorbing state, meaning that patients cannot transition out of the health state upon entering.

B.3a.2.4 Transitions

Patient transitions are time-dependent and assessed each cycle:

- **Transitions from the PF state to the PD state** are informed by time-to-progression (TTP) curves for each treatment.

- **Transitions from the PF state to death** are informed by pre-progression survival (PrePS) curves from SEQUOIA and constrained by age- and gender-matched UK general population mortality to ensure the disease-related risk of death does not exceed general population.

- **Transitions from the PD state to death** are informed by post-progression survival (PPS) curves from the MURANO study and constrained by age- and gender-matched UK general population mortality to ensure the disease-related risk of death does not exceed general population. As post-progression data from SEQUOIA trial was considered too immature at the latest data cut-off of 07 March 2022 (only 23 [9.5%] deaths had occurred in zanubrutinib arm A at this time), published data sources were leveraged and extrapolated to provide clinically meaningful long-term survival estimation.

Time on first-line treatment is modelled independently from TTP and PrePS, allowing patients to discontinue treatment despite remaining in the PF state. Time on first-line treatment is constrained by TTP, reflecting that BTKi treatment should be administered until disease progression or unacceptable toxicity. In addition, time on second-line treatment is modelled independently from PPS, allowing patients to complete or discontinue treatment despite remaining in the PD state. PFS for second-line treatment is derived from the same published data sources as PPS and used as a proxy to estimate the time on subsequent treatment in combination with treatment specific stopping rules. Treatment-related costs, such as drug acquisition and drug administration costs, are accrued based on the time on treatment.

Model conceptualisation and justification for approach

Whilst the partitioned survival approach is commonly used and well accepted in oncology appraisals, the state transition semi-Markov approach was deemed more appropriate in modelling outcomes for patients with previously untreated CLL for the following reasons:

- Partitioned survival models (PSMs) require relatively mature long-term OS data, which were not available from SEQUOIA. Without mature data, both the resulting predictions of long-term survival and the assessment of treatment effects beyond the trial period are subject to considerable uncertainty. In comparison, the semi-Markov approach is not dependent on OS and allows more explicit use of information on

intermediate endpoints, such as PrePS and PPS, to inform mortality calibration. Furthermore, the structure allows the use of published data sources to inform post-progression outcomes, which allow the treatment effect of subsequent lines of therapy to be modelled with treatment-specific data.

- The partitioned survival approach will produce reliable predictions only when the OS model used represents changing hazards observed within the trial and can predict how changing health state membership will drive mortality hazards beyond the trial period for each treatment.[85] To reflect the indolent nature of previously untreated CLL, where patients follow a pathway from the treatment-naïve setting (i.e., first-line treatment) to the R/R setting (i.e., second-line treatment), state transition Markov approach allows explicitly modelling the second-line treatment impact on post-progression hazards and implicitly capturing any effect thereafter.

- Adopting a state transition modelling approach avoids potential logical inconsistencies that may occur in a PSM, such as independently extrapolated long-term OS based on immature trial data exceeding the age-matched general population survival, or the crossing of independently extrapolated PFS and OS curves, which would lack face validity and otherwise force adjustments to be made in the model.

- The semi-Markov approach allows more granular disease modelling and event rates to be specified for individual components of the disease process, which improves transparency and facilitates meaningful long-term extrapolations and sensitivity analyses.

Since discrete event simulation models are highly data intensive, this approach was not considered feasible given the limited clinical efficacy data available. Clinical and economic experts in attendance at an advisory board (03 November 2022) held by the Company deemed the semi-Markov model structure suitable for the decision problem.[11]

B.3a.2.5 Intervention technology and comparators

The intervention in the model is zanubrutinib. As highlighted in Section B.1.1.1 Comparators, acalabrutinib and ibrutinib (‘high-risk’ patients only) are considered the key relevant comparators to zanubrutinib in patients with previously untreated CLL. This is supported by

the 2022 BSH guidelines for the treatment of CLL, by UK clinical expert opinion in 1:1 interviews and an advisory board (03 November 2022) conducted by the Company.[10,11,105] Details of the dosing used in the model can be found in Table 69.

Table 69: Dosing regiments in the economic model

Drug	Dosing regimen	Source
Zanubrutinib	320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or unacceptable toxicity	Zanubrutinib SmPC[2]
Ibrutinib	420 mg administered orally once daily until PD or unacceptable toxicity	Ibrutinib SmPC[106]
Acalabrutinib	100 mg administered orally twice daily until PD or unacceptable toxicity	Acalabrutinib SmPC[107]

PD – Progressed disease; SmPC – Summary of Product Characteristics.

B.3a.3 Clinical parameters and variables

Individual survival analyses were required to estimate transitions between health states. The key clinical parameters and variables in the model which required separate survival analyses were:

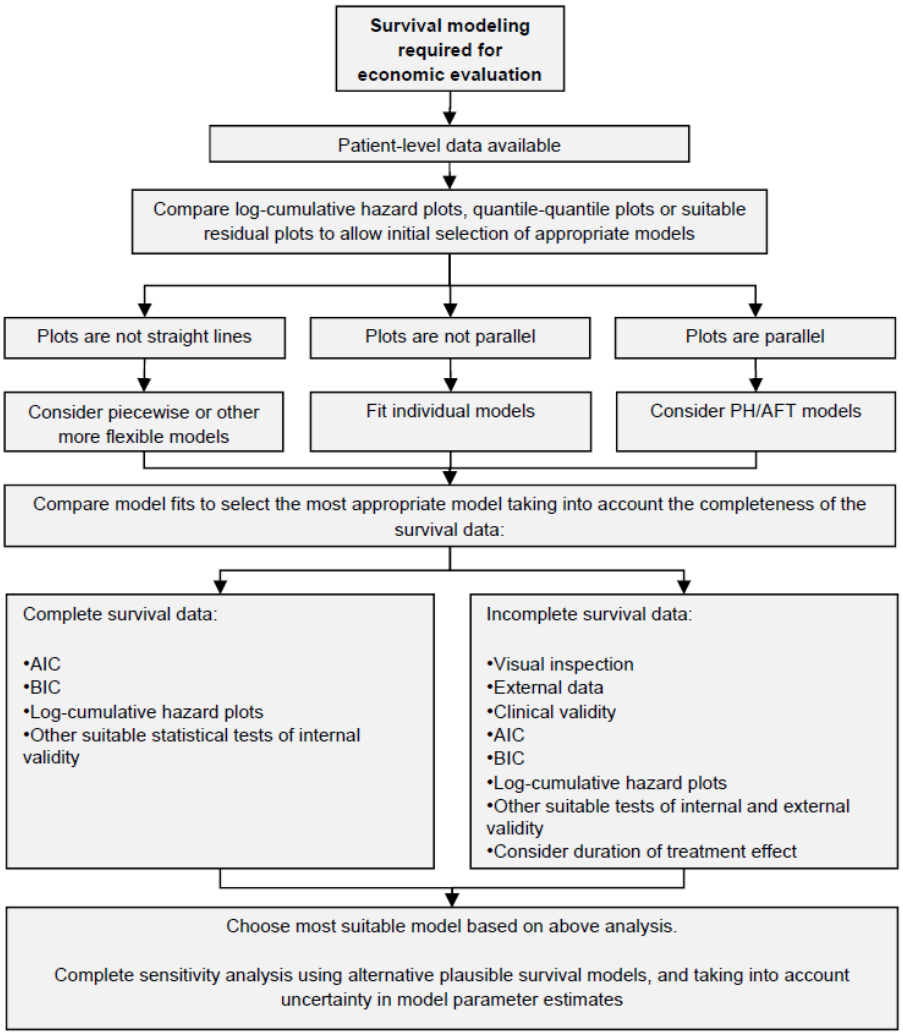
- TTP (deaths considered censored events in the PFS dataset)
- PrePS (progression events considered censored events in the PFS dataset)
- PPS
- TTD (for cost calculations only)
- PFS in 2L (for cost calculations only)

B.3a.3.1 Time to event analysis

Parametric survival analysis was conducted by fitting survival functions to patient-level survival data from in SEQUOIA to estimate long-term extrapolations. The survival analysis was conducted in line with the methods recommended by NICE DSU 14, using the following distributions: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma.[85]

As summarised in Figure 45, the process of selecting a best-fitting distribution involved an assessment of clinical plausibility leveraging clinical expert opinion and comparing to real-world data, coupled with an assessment of statistical fit via measures such as Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). The extrapolated curves were also visually compared against the KM data from SEQUOIA to assess fit over the observed data period. The most clinically plausible and best-fitting models were selected for the model base-case with the impact of selecting alternative curves considered in sensitivity analysis.

Figure 45: Survival Model Selection Process Algorithm Presented by NICE DSU TSD-14, and Referenced by Other HTA Agencies



AFT – Accelerated failure time; AIC – Akaike information criterion; BIC – Bayesian information criterion; DSU – Decision Support Unit; HTA – Health technology assessment; NICE – National Institute for Health and Care Excellence; PH – Proportional hazards.

B.3a.3.2 Pre-progression

To align with the MAIC analyses performed (see Section B.2.9 Indirect and mixed treatment comparisons), pooled zanubrutinib data from SEQUOIA (arm A and arm C) were used for the base case survival extrapolations for zanubrutinib. The pooled survival data reflects the full Cohort of previously untreated patients with CLL both with and without a 17p deletion and/or TP53 mutation and was used to model survival for both 'unfit' and 'high-risk' patients within the base-case analyses. Scenario analyses were conducted using data from SEQUOIA arm A in the 'unfit' population and arm C in the 'high-risk' population with details of the extrapolations and curve selection presented in Appendix M.

As IRC-assessed PFS was the primary outcome in SEQUOIA, extrapolations based on the IRC-assessed endpoint are presented in the base case, with extrapolations using the INV-assessed endpoint presented as a scenario analysis. Details of INV-assessed TTP and PrePS KM curves and parametric model statistics are provided in Appendix M.

B.3a.3.2.1 TTP (pooled SEQUOIA arm A and arm C population)

TTP was directly derived from individual patient-level data (IPD) from the pooled population of arm A and arm C of the SEQUOIA trial. As of the data cut-off of 07 May 2021, 27 (11.2%) patients treated with zanubrutinib in arm A and 14 (12.7%) patients treated with zanubrutinib in arm C had experienced IRC-assessed disease progression.

Survival functions as per the NICE DSU guidelines were fitted to the TTP patient-level data. The goodness-of-fit statistics for the IRC-assessed TTP endpoint for zanubrutinib (pooled SEQUOIA arm A and arm C population) are presented in Table 70. Based on the AIC and BIC statistics, the log-normal distribution provided the best statistical fit (AIC) to the observed data for zanubrutinib, and the log-logistic distribution provided the second-best statistical fit (AIC). However, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.[108]

Table 70: Goodness-of-fit statistics for IRC-assessed TTP – zanubrutinib (pooled SEQUOIA arm A and arm C)

Distribution	Zanubrutinib (Stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; IRC – Independent review committee; TTP – Time-to-progression. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for IRC-assessed TTP for zanubrutinib (pooled SEQUOIA arm A and arm C population) are presented in Figure 46. The Gompertz model provides the most conservative estimations, followed by the Weibull model. The remaining parametric functions exhibit tails which plateau.

Figure 46: KM for IRC-assessed TTP overlaid with extrapolated parametric survival curves – zanubrutinib (pooled SEQUOIA arm A and arm C)

KM – Kaplan-Meier; IRC – Independent review committee; TTP – Time-to-progression

Sole assessment of the visual and statistical fit of the TTP curves was not sufficient to determine the distribution for TTP and additional clinical validation of the curve selection was required, which is discussed in Section B.3a.3.2.3 Base-case curve selection for TTP and PrePS (pooled SEQUOIA arm A and arm C population).

B.3a.3.2.2 PrePS (pooled SEQUOIA Cohort 1 and Cohort 2)

A low number of pre-progression death events were observed across both Cohort 1 (arm A and arm B) and Cohort 2 (arm C) of the SEQUOIA trial, and as such, data across all three arms were used to inform the PrePS extrapolation. To achieve this, extrapolated curves from

pooled arm A and arm C were averaged with extrapolated curves from arm B. As of the cut-off of 07 May 2021, only 9 (3.7%) patients treated with zanubrutinib in arm A, 12 (5.0%) patients treated with BR in arm B, and 1 (0.9%) patient treated with zanubrutinib in arm C died prior to disease progression.

The goodness-of-fit statistics for the IRC-assessed PrePS endpoint for zanubrutinib (pooled SEQUOIA Cohort 1 and Cohort 2) are presented in Table 71. Based on the AIC and BIC statistics, the exponential distribution provided the best statistical fit (AIC) to the observed data for zanubrutinib in both pooled arm A and arm C, and for BR in arm B. However, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.[108]

Table 71: Goodness-of-fit statistics for IRC-assessed PrePS (pooled SEQUOIA Cohort 1 and Cohort 2 for zanubrutinib and Cohort 1 for bendamustine-rituximab)

Distribution	Zanubrutinib (pooled arm A and arm C)		Bendamustine-rituximab (arm B)	
	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; IRC – Independent review committee; PrePS – Pre-progression survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for IRC-assessed PrePS for zanubrutinib (pooled SEQUOIA arm A and arm C population) and BR (arm B) are presented in Figure 47 and Figure 48, respectively. The Gompertz model provides the most conservative estimations for the pooled arm A and arm C, with the remaining parametric functions exhibiting tails which plateau; for arm B the curves, all exhibit tails which plateau.

Figure 47: KM for IRC-assessed PrePS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled SEQUOIA arm A and arm C) over 10 years

IRC – Independent review committee; KM – Kaplan-Meier; PrePS – Pre-progression survival.

Figure 48: KM for IRC-assessed PrePS overlaid with extrapolated parametric survival curves – bendamustine (arm B) over 10 years

IRC – Independent review committee; KM – Kaplan-Meier; PrePS – Pre-progression survival.

Sole assessment of the visual and statistical fit of the PrePS curves was not sufficient to determine the distribution for PrePS and additional clinical validation of the curve selection was required, which is discussed in Section B.3a.3.2.3 Base-case curve selection for TTP and PrePS (pooled SEQUOIA arm A and arm C population).

To ensure validity, PrePS was constrained by UK general population mortality (matched on age and gender), which was applied as a competing risk of death. Due to the low number of events in SEQUOIA, the extrapolations for PrePS are informed by general population mortality for most of the model time horizon. This assumption was validated by clinical and economic experts in attendance at an advisory board (03 November 2022) held by the Company.[11] An illustrative example is provided in Figure 49 to demonstrate age- and gender-matched UK general population mortality overtaking the extrapolated extrapolations for PrePS, with mortality risk increasing smoothly up to ~62 months before changing to a stepwise increase.

Figure 49: Illustrative demonstration of general population mortality being applied as a competing risk of death to PrePS

PrePS – Pre-progression survival; UK – United Kingdom.

B.3a.3.2.3 Base-case curve selection for TTP and PrePS (pooled SEQUOIA arm A and arm C population)

Feedback received from an advisory board conducted by the Company (03 November 2022) highlighted that ~60% of patients would be expected to be progression-free at 8 years, based on long-term data from ibrutinib trials (RESONATE-2) in the first-line setting.[11,109] As PFS is comprised of TTP and PrePS, a decision was made to align the distributions used to extrapolate TTP and PrePS to provide a better representation of PFS. In order to identify the most plausible extrapolations, the statistical fit and predicted long-term survival outputs from the model were compared.

As shown in Table 72:, the log-normal and exponential curves were the best statistically fitting models for TTP and PrePS, respectively, and no distribution was outside of the zero-four-AIC point threshold for both TTP and PrePS.

Table 72: AIC for IRC-assessed TTP and PrePS – zanubrutinib (pooled SEQUOIA arm A and arm C)

Distributions	TTP	PrePS
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

AIC – Akaike information criterion; IRC – Independent review committee; PrePS – Pre-progression survival; TTP – Time-to-progression. **Bold indicates the distribution with the best statistical fit.**

Landmark PFS rates for zanubrutinib are presented in Table 73. The generalised gamma distribution produced extrapolations at which ~60% of patients were progression-free at 8 years in line with the rates stated by clinical experts in an advisory board conducted by the Company (03 November 2022).[11] Therefore, the generalised gamma model was selected to inform the TTP and PrePS extrapolations in the base case. Sensitivity analyses were conducted using the next two closest curves (log-normal and exponential) to 60% PFS at 8 years. These curves also correspond to the best statistically fitting curves for TPP and PrePS.

Table 73: Landmark PFS using equalised parametric distributions for IRC-assessed TTP and PrePS – zanubrutinib (pooled SEQUOIA arm A and arm C)

Distribution	Median (years)	PFS (%) at landmark timepoints						
		1-year	5-year	8-year	10-year	15-year	20-year	30-year
Weibull	[redacted]							
Log-normal	[redacted]							
Log-logistic	[redacted]							
Exponential	[redacted]							
Generalised Gamma	[redacted]							
Gompertz	[redacted]							

IRC – Independent review committee; PFS – Progression-free survival; PrePS – Pre-progression survival; TTP – Time-to-progression.

B.3a.3.2.4 Treatment duration

The model base case assumes that all BTKis are given until progression in line with the respective SmPCs. This assumption was validated by UK clinical experts in attendance at an advisory board (03 November 2022) organised by the Company.[11]

An alternative approach of modelling extrapolated TTD data from SEQUOIA for zanubrutinib was explored and presented as a scenario analysis. No TTD data were available in the literature for ibrutinib and acalabrutinib, so no alternative approaches were explored for these treatments.

Details of the TTD KM curves, diagnostic plots, and parametric model statistics are provided in Appendix M.

B.3a.3.3 Post-progression

Following disease progression, patients move onto subsequent therapies that are determined by the first-line treatment taken. Due to the limited number of patients with progressive disease in SEQUOIA, published data sources were reviewed and used to inform the PPS modelling. Quantitative prescribing data from December 2022 collected by IQVIA, as well as feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews, and from UK clinical experts in attendance at an advisory board (03 November 2022) both conducted by the Company suggested that a treatment 'sequencing' approach was used in clinical practice.[7,10,11] Following progression on a front-line BTKi, a BCL2i regimen is typically recommended, regardless of which BTKi is initially prescribed, with venetoclax-rituximab being considered the venetoclax regimen of choice.[10,11] Further details on the sequencing approach to the treatment pathway and the choice between a BTKi and venetoclax-based regimens is discussed in Section B.1.1.1 Comparators.

In line with the anticipated treatment pathway for patients with CLL based on clinical feedback, the MURANO study was deemed the most appropriate data source to inform PPS and duration of subsequent treatment in the model. IPD were reconstructed from the clinical trial published KM curves before parametric survival curves were fitted according to the methods described in B.3a.3.1 Time to event analysis. The choice of the MURANO study was validated by UK clinical experts in attendance at an advisory board (03 November 2022) held by the Company.[11]

To align with the use of MURANO to inform PPS and duration of subsequent treatment, the percentage of patients receiving subsequent treatment after progression was assumed to be 100% with all patients receiving venetoclax-rituximab. This assumption was validated by UK clinical experts at an advisory board (03 November 2022) conducted by the Company.[11]

B.3a.3.3.1 Post-progression survival (PPS)

MURANO was a randomised, open-label, phase III study that evaluated the efficacy of venetoclax-rituximab (venetoclax up to 2 years; rituximab for six 28-day cycles) compared to BR (both bendamustine and rituximab for six 28-day cycles) in 389 previously treated patients with R/R CLL. At the five-year data cut, with a median follow-up of 59 months (range: 0 to 71.5), 82.1% of patients treated with venetoclax-rituximab were still alive compared to 62.2% of patients treated with BR (HR: 0.40, 95% CI: 0.26, 0.62).[110]

Survival functions as per the NICE DSU guidelines were fitted to MURANO PPS to extrapolate long-term survival. The goodness-of-fit statistics for the OS endpoint for the venetoclax-rituximab arm in MURANO are presented in Table 74. Based on the AIC and BIC statistics, the exponential distribution provided the best statistical fit (AIC) to the observed data for venetoclax-rituximab, and the Weibull distribution provided the second-best statistical fit (AIC). However, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.

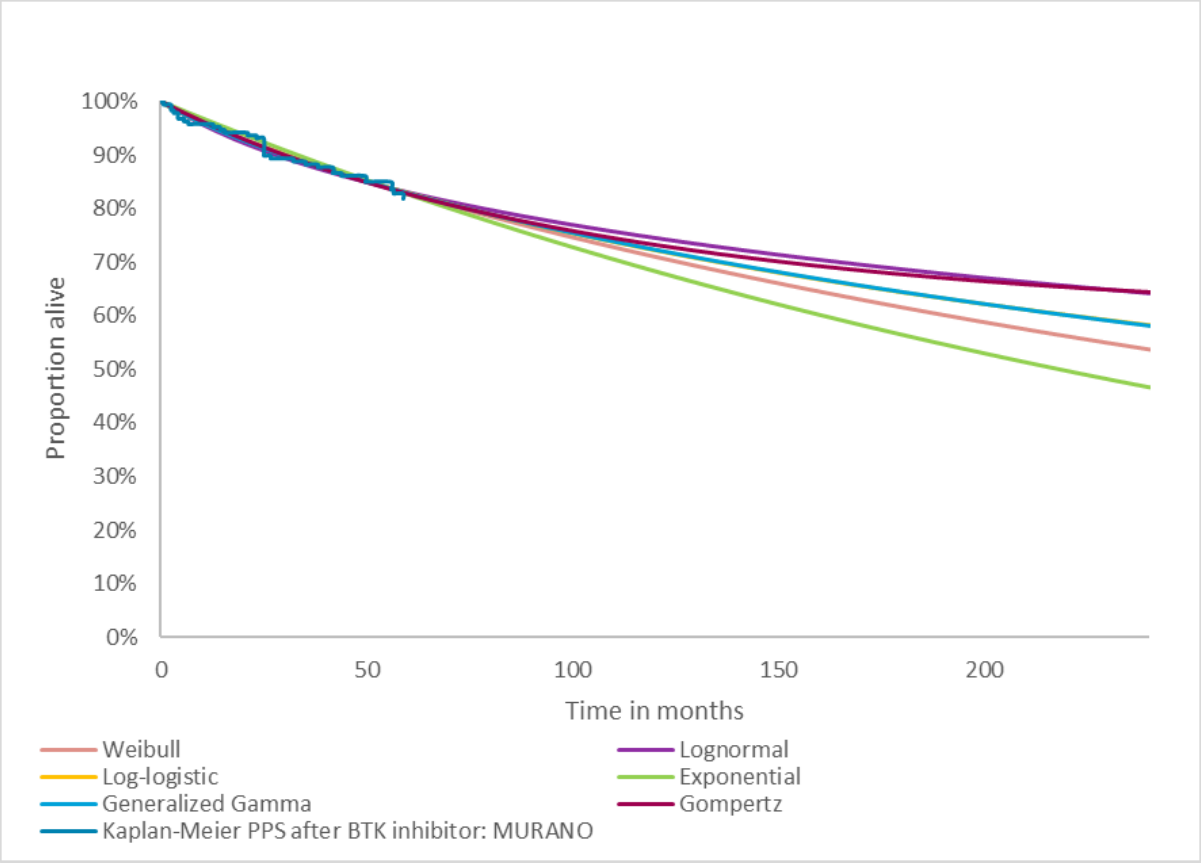
Table 74: Goodness-of-fit statistics for PPS – venetoclax-rituximab (MURANO)

Distribution	Venetoclax-rituximab	
	AIC	BIC
Weibull	529.48	217.54
Log-normal	529.71	216.62
Log-logistic	529.50	217.39
Exponential	**528.25**	**216.51**
Generalised Gamma	531.51	219.90
Gompertz	529.75	218.20

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; PPS – Post-progression survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for OS venetoclax-rituximab (MURANO) are presented in Figure 50. All extrapolations were similar with the exponential distribution providing the most conservative extrapolations and Gompertz providing the most optimistic estimation. As the exponential distribution provided the best statistical fit and there is no strong evidence of an increasing risk before general population mortality is applied, it was selected to inform the base case.

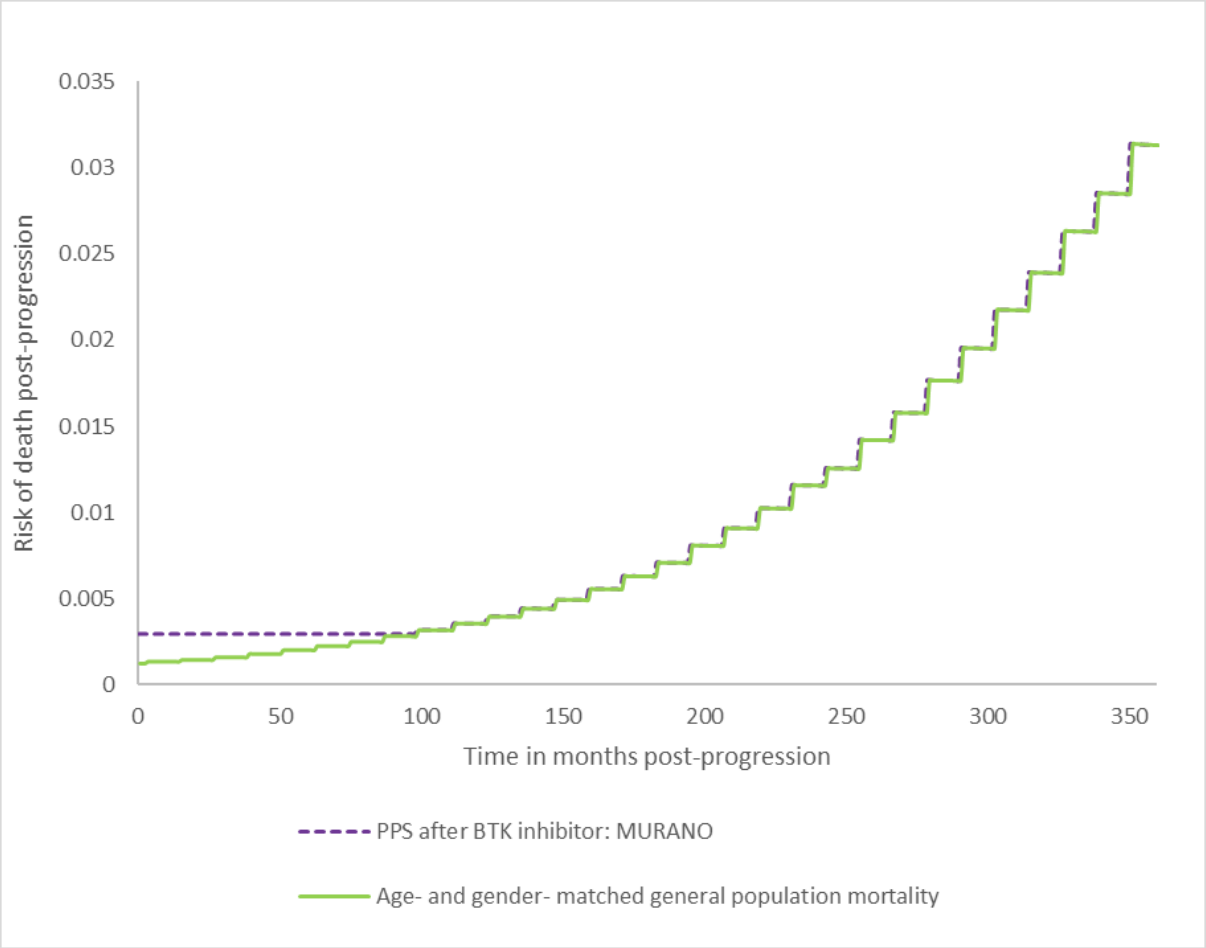
Figure 50: KM for PPS overlaid with extrapolated parametric survival curves – venetoclax-rituximab (MURANO)



BTK – Bruton tyrosine kinase; KM – Kaplan-Meier; PPS – Post-progression survival.

To ensure validity, PPS was constrained by UK general population mortality (matched on age and gender), which was applied as a competing risk of death. UK clinical experts in an attendance at an advisory board (03 November 2022) deemed this assumption as appropriate.[11] Furthermore, clinical expert opinion indicated that the exponential curve was reasonable to extrapolate data from MURANO to inform PPS. The choice of PPS curve is not a large driver of the model results; however, the model includes functionality to select any of the six standard parametric curves and hence alternative curves are explored in sensitivity analyses. An illustrative example is provided in Figure 51 to demonstrate age- and gender-matched UK general population mortality overtaking the extrapolated extrapolations for PPS, with mortality risk increasing smoothly up to ~100 months before changing to a stepwise increase.

Figure 51: Illustrative demonstration of general population mortality being applied as a competing risk of death to PPS



BTK – Bruton tyrosine kinase; PPS – Post-progression survival.

B.3a.3 .3.2 PFS in 2L

To align with the PPS data source, PFS data from MURANO was used to determine time on second-line treatment. The PFS data does not inform patient movement and is only used to determine treatment costs associated with subsequent treatments. At the five-year cut-off, with a median follow-up of 59 months (range: 0 to 71.5), median PFS was 53.6 months for patients treated with venetoclax-rituximab compared to 17.0 months for patients treated with BR HR: 0.19, 95% CI: 0.15, 0.26).[110]

The goodness-of-fit statistics for the PFS endpoint for the venetoclax-rituximab arm in MURANO are presented in Table 75. Based on the AIC and BIC statistics, the Gompertz distribution provided the best statistical fit (AIC) to the observed data for venetoclax-rituximab, and the generalised gamma distribution provided the second-best statistical fit (AIC). Only the generalised gamma curve was within four AIC points of the best fitting curve.

Table 75: Goodness-of-fit statistics for PFS in 2L – venetoclax-rituximab (MURANO)

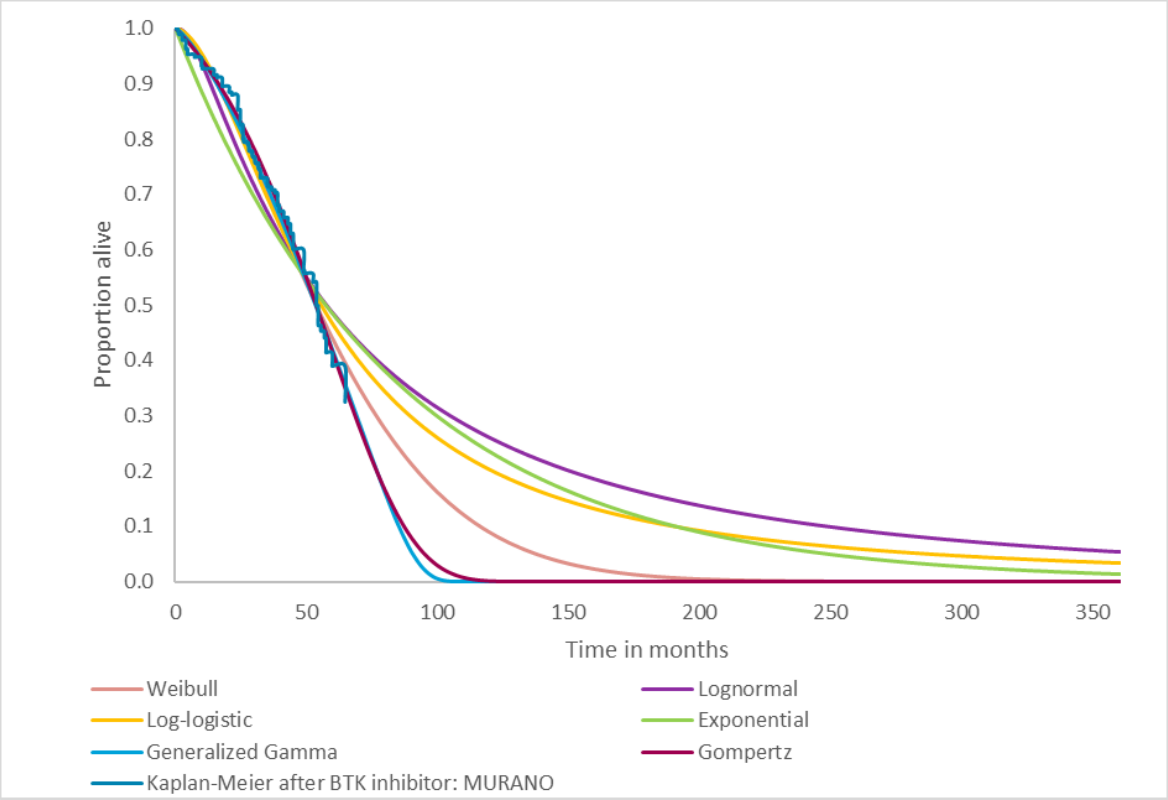
Distribution	MURANO venetoclax-rituximab	
	AIC	BIC
Weibull	1,333.93	1,340.40
Log-normal	1,355.74	1,362.21
Log-logistic	1,341.09	1,347.56
Exponential	1,351.39	1,354.64
Generalised Gamma	1,331.10	1,340.78
Gompertz	**1,327.37**	**1,333.85**

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; PFS – Progression-free survival; 2L – Second-line. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for PFS venetoclax-rituximab (MURANO) are presented in Figure 52. The generalised gamma and Gompertz distributions provided the most conservative extrapolations with all patients progressing within ~110 months. In comparison, the log-normal provided the most optimistic extrapolation with 10% of patients' progression-free at ~350 months. Feedback received from an advisory board conducted by the Company (03 November 2022) highlighted that a lower PFS was expected following progression on a BTKi in an elderly population and as such, the Gompertz distribution was selected to inform the base case.[11]

To ensure validity, PFS in 2L was constrained by the extrapolated PPS. Furthermore, a cap was applied to treatment such that patients did not receive more than the SmPC stated dose i.e. venetoclax for a maximum duration of 2 years and rituximab for a maximum duration of six 28-day cycles.[111]

Figure 52: KM for PFS in 2L overlaid with extrapolated parametric survival curves – venetoclax-rituximab (MURANO)



BTK – Bruton tyrosine kinase; KM – Kaplan-Meier; PPS – Post-progression survival; 2L – Second-line.

B.3a.3.4 Relative efficacy

B.3a.3.4.1 Comparison with acalabrutinib in 'unfit' and 'high-risk' patients

As discussed in Section B.2.9 Indirect and mixed treatment comparisons , a MAIC was conducted which demonstrated that zanubrutinib is at least non-inferior to acalabrutinib ([redacted]) in patients with previously untreated CLL who are unsuitable for FCR and BR therapy, irrespective of the presence of a 17p deletion and/or TP53 mutation. Feedback received from an advisory board conducted by the Company (03 November 2022) agreed that the HRs were **clinically plausible** and noted that the similarity between the unadjusted and adjusted PFS and OS KMs for zanubrutinib and acalabrutinib supported the non-inferiority of zanubrutinib to acalabrutinib.[11]

In TA429 and TA689, NICE provided a recommendation for acalabrutinib and ibrutinib, respectively, in patients with previously untreated adults CLL who have a 17p deletion or

TP53 mutation and in whom CIT is unsuitable based on data presented in patients with R/R CLL. Two MAICs have been conducted comparing outcomes on zanubrutinib with acalabrutinib in patients with R/R CLL as described in Section B.2.9 Indirect and mixed treatment comparisons . The MAICs conducted using ELEVATE-RR and ASCEND contained a high proportion of patients with a 17p deletion or TP53 mutation (~40% each), these analyses are deemed highly relevant as a proxy for previously untreated patients with 17p deletion and/or TP53 mutation.

The MAICs presented make the best use of the available evidence for zanubrutinib and acalabrutinib**.** The MAIC conducted in the previously untreated population, coupled with MAICs conducted in the R/R population, support the conclusion that zanubrutinib is at least non-inferior to acalabrutinib across both the previously untreated ‘unfit’ and ‘high-risk’ populations.

Therefore, as discussed in Section B.3a.2 Economic analysis a CMA was conducted versus acalabrutinib which assumed equivalence of zanubrutinib to acalabrutinib across all time to event endpoints.

B.3a.3 .4.2 Comparison with ibrutinib in ‘high-risk’ patients

Ibrutinib is only approved by NICE in previously untreated 'high-risk’ patients with CLL.[88] As there is a paucity of evidence specifically reported in patients with a 17p deletion and/or TP53 mutation, there was insufficient data to conduct a MAIC versus ibrutinib in the previously untreated ‘high-risk’ population, with both of the key phase 3 clinical trials (RESONATE-2 and ALLIANCE) only including a minority of patients with these ‘high-risk’ factors.

With data in patients with R/R CLL having been previously accepted by NICE as a proxy to support reimbursement decisions in this population, head-to-head results comparing zanubrutinib with ibrutinib from the ALPINE trial were deemed highly relevant in this population.[78,88] Zanubrutinib is associated with a statistically significant 45% reduction in the risk of INV-assessed disease progression or death at data cut-off of 01 December 2021 (HR: 0.55, 95% CI: 0.39-0.76) and statistically significant 39% reduction in the risk of IRC-assessed disease progression or death (HR:0.61; 95% CI: 0.44, 0.86). Furthermore, late breaking PFS data with a median follow up of 29.6 months (DCO: 08 August 2022), showed a statistically significant 35% reduction in the risk of disease progression or death for

zanubrutinib compared with ibrutinib (HR: 0.65; 95% CI: 0.49, 0.86 for both INV- and IRC-assessed PFS).[77]

When assessing outcomes in patients with 17p deletion or TP53 mutations specifically (DCO 01 December 2021), zanubrutinib was associated with a [redacted]% reduction in the risk of INV-assessed disease progression or death ([redacted]) and statistically significant [redacted]% reduction in the risk of IRC-assessed disease progression or death ([redacted]).

To supplement the comparison with ibrutinib, a naïve comparison was conducted to assess the efficacy of zanubrutinib versus ibrutinib in patients with untreated CLL comparing high-risk specific data from Mato et al. (2018) with Cohort 2 (arm C) of SEQUOIA. Based on the naïve comparison, there was no statistically significant difference in PFS between zanubrutinib and ibrutinib ([redacted]), however a numerical improvement following treatment with zanubrutinib was observed. Furthermore, there was a statistically significant difference in OS between zanubrutinib and ibrutinib ([redacted]).

As such, it is clinically plausible to conclude that the zanubrutinib will be at least non-inferior to ibrutinib in previously untreated 'high-risk' patients. This conclusion was deemed conservative but clinically plausible by UK clinical experts in attendance at an advisory (03 November 2022) held by the Company.[11]

Therefore, as discussed in Section B.3a.2 Economic analysis a CMA was conducted versus ibrutinib which assumed equivalence of zanubrutinib to ibrutinib across all time to event endpoints.

B.3a.3 .4.2 Assessment of uncertainty

To model non-inferiority, the following steps were taken:

- A HR of 1 (versus zanubrutinib) was assumed for both acalabrutinib and ibrutinib for TTP.
- Equivalent PrePS was applied across zanubrutinib, ibrutinib and acalabrutinib as informed by SEQUOIA Cohort1 and Cohort 2.

- Time on treatment was assumed to be equal across zanubrutinib, acalabrutinib and ibrutinib with all BTKis modelled to be given until progression.

- Equivalent PPS and PFS in 2L was applied for zanubrutinib, ibrutinib and acalabrutinib, reflecting the assumption that patients who progress on a BTKi will receive treatment with a venetoclax-based regimen as the next line of treatment.

The sensitivity of the results of the CMA approach, assuming equal efficacy of zanubrutinib compared to acalabrutinib and ibrutinib, respectively, was explored within probabilistic and deterministic sensitivity analyses, as per the NICE methods guides.[112] Furthermore, cost-utility analyses are also explored in which the PFS HR generated in the MAICs and the naïve comparison versus Mato et al. (2018) are applied to the TTP endpoint.

B.3a.3.5 Summary of base-case inputs

The data sources and chosen distributions or parameters to inform the base case are presented in Table 76.

Table 76: Data sources and distributions used to inform base case clinical parameters

Clinical parameter	Data source	Chosen distribution/input
TTP	SEQUOIA for zanubrutinib, HR=1 applied for acalabrutinib and ibrutinib	Generalised gamma
PrePS	SEQUOIA for all BTKis	Generalised gamma
TTD	SEQUOIA for all BTKis	Until treatment progression
PFS in 2L	MURANO PFS for all BTKis	Exponential
PPS	MURANO OS for all BTKis	Gompertz

BTKi – Bruton tyrosine kinase inhibitor; HR – Hazard ratio; OS – Overall survival; PPS – Post-progression survival; PrePS – Pre-progression survival; TTD – Time to treatment discontinuation; TTP – Time-to-progression; 2L – Second-line.

B.3a.4 Measurement and valuation of health effects used for scenario analyses

Patients with CLL typically experience worse HRQoL compared to the general population across several domains, including symptom burden, mental functioning, and physical functioning. See Section B.1.3.2 Burden of CLL for further information.

B.3a.4.1 Health-related quality of life data from clinical trials

The SEQUOIA trial collected HRQoL data using EQ-5D-5L at baseline and every 12 weeks from the start of Cycle 1 for 96 weeks and then every 24 weeks until disease progression.

B.3a.4.2 Mapping

In line with the NICE reference case, the EQ-5D-5L indices were then mapped to EQ-5D-3L indices using the crosswalk algorithm published by Hernandez-Alava (2022) to generate utility scores.[112,113] Once mapped, the EQ-5D-3L utility scores at all visits were analysed using a mixed-effects linear regression with a random intercept for each patient to account for repeated measures. The potential effect of treatment and progression status on utility was explored both individually, and jointly in the same model. All regression models were adjusted for baseline utility (centred at the mean value of the eligible population) to consider between-patient differences in utilities at baseline.

As there was no evidence of systematic differences in QoL across study arms, the utility values generated by pooling across treatments were deemed most appropriate to inform the model to increase the sample size of the analysis. The mean EQ-5D utility scores from SEQUOIA are presented by treatment and visit in Figure 53.

Figure 53: Trial generated EQ-5D per treatment and visit – SEQUOIA (arm A and arm B)

BR – Bendamustine-rituximab; EQ-5D – EuroQoL Five Dimensions.

The predicted utility for each health state from the model compared to utilities based on published general population in the UK is presented in Table 77. Progression was assessed by IRC to align with the primary endpoint of SEQUOIA. The mean PF and PD utility scores

were higher than the estimates for age-matched, condition-stratified UK general population. As such, the utility values from SEQUOIA trial lack face validity with results potentially impacted by immaturity of data. This issue also occurred in NICE TA689, in which utility values generated from ELEVATE-TN were also higher than the age- and gender-matched UK population.[78]

Table 77. Utility Model Including Progression Status as Predictors

Predictor	No. of Patients	No. of Obs.	Coefficient (95% CI)	Source
Predicted utility for health states				
PF	[redacted]	[redacted]	[redacted]	SEQUIOA
PD	[redacted]	[redacted]	[redacted]	
Mean utility based on published general population in UK				
General population irrespective of health status (65 to ⩽70)			0.804 (0.790, 0.817)	Ara and Brazier 2011[45]; supplementary Table A4
General population with health condition "cancer" (65 to ⩽70)			0.730 (0.652, 0.807)	
General population without health condition "cancer" (65 to ⩽70)			0.808 (0.794, 0.821)	

*5 out of 420 eligible patients were removed from the analysis due to missing progression status. CI - confidence interval; PD - progressed disease; PF - progression-free; UK - United Kingdom.

B.3a.4.3 Health-related quality of life studies

An SLR was conducted to identify studies reporting on the HRQoL of patients with previously untreated CLL or patients with R/R CLL. Full details of the process and methods used to identify and select the HRQoL data relevant to the technology being evaluated are presented in Appendices H.

For HRQoL publications, only studies which included BTKi treatments (zanubrutinib, ibrutinib and acalabrutinib) were extracted (n=10 [eight identified through database searches and two NICE HTA submissions identified through grey literature searches]). A summary of these studies is provided in Table 78.

Table 78: Summary of published HRQoL studies

Data source	Patient population	Method of elicitation	Utility measure	Utility value	
				PF health state	PD health state
Alrawashdh (2022)[114]	Patients with CLL	Not reported	Mean value (SD)	PFS without therapy: 0.82 (0.17) PFS without second-line therapy: 0.71 (0.23) PFS on initial therapy oral treatment: 0.71 0.20) PFS on initial therapy IV treatment: 0.67 (0.22) PFS on targeted therapy: 0.799 (0.20) PFS on second-line therapy: 0.55 (0.25) PFS on initial therapy with increased hospital visits: 0.55 (0.26)	Progression after first-line treatment: 0.66 (0.22) Relapsed lines of treatment: 0.42 (0.25)
Sinha (2018)[96]	Untreated patients (18 years or older) with CLL with comorbidities	Not reported	Mean value (SD)	Oral Treatment: 0.71 (0.20) IV Treatment: 0.67 (0.22) I.V. Treatment With More Hospital Visits: 0.55 (0.26) After Treatment: 0.82 (0.17)	After First-Line Treatment: 0.66 (0.22) Relapsed Treatment Lines: 0.42 (0.25)
Barnes (2018)[115]	Patients with CLL older than age 65 years without a 17p deletion	Not reported	QALYs per life-year	PFS on initial therapy Ibrutinib: 0.71 Comparator: 0.67 PFS not on therapy after initial therapy Comparator: 0.82 PFS on second-line therapy, Both: 0.55	Progressed, awaiting second-line therapy, Both: 0.66 Progressed, awaiting third-line therapy, Both: 0.59 Receiving best supportive care/hospice, Both: 0.59

Data source	Patient population	Method of elicitation	Utility measure	Utility value	
				PF health state	PD health state
				PFS completed second-line therapy, Both: 0.71 PFS on third- or greater-line therapy, Both: 0.42 PFS completed third-line therapy, Both: 0.59	
Osorio (2021)[116]	Adult patients with CLL with indication to start single-agent ibrutinib therapy, as first-line or following prior therapies	EQ-5D-5L questionnaire	Mean baseline (SD)	0.90 (0.12)	NR
Barr (2018)[45]	Patients with CLL aged ≥65 years receiving 420 mg ibrutinib once daily until PD or chlorambucil for up to 12 months	EQ-5D-5L questionnaire	PRO measurements showed significantly greater improvements over time with ibrutinib vs chlorambucil in EQ-5D-5L Visual Analogue Scale (P=0.0004) by repeated measure analysis.		
Patel (2020)[117]	Previously untreated CLL patients	Not reported	Mean (range)	PFS, oral treatment: 0.71, range: 0.67-0.75 PFS, IV treatment: 0.67, range: 0.63-0.71 PFS, no treatment (after first-line): 0.82, range: 0.78-0.85 PFS, no treatment (after second-line or later): 0.71, range: 0.66-0.75 PFS, third-line therapy: 0.55, range: 0.50-0.60	Relapsed lines of treatment: 0.42, range: 0.37-0.47

Data source	Patient population	Method of elicitation	Utility measure	Utility value	
				PF health state	PD health state
				PFS, fourth-line therapy: 0.42, range: 0.37-0.47	
Cheung (2021)[118]	Previously untreated older patients with CLL	Canadian EQ-5D-5L value set	Mean score Bendamustine-rituximab (N = 18)/ Ibrutinib (N = 17)/ Ibrutinib-rituximab (N=18)	Baseline: 0.90/ 0.87/ 0.88 Month 3: 0.88/ 0.80/ 0.78 Month 6: 0.88/ 0.85/ 0.82 Month 9: 0.88/ 0.85/ 0.87 Month 24: 0.85/ 0.87/ 0.87	NR
Singh (2017)[119]	Patients with untreated CLL and ineligible for full-dose chemo-immunotherapy	Not reported	Mean score	PFS without therapy lines: 0.82	NR
NICE TA689[78]	Adult patients with untreated and treated CLL Mean age: untreated – 70 years; treated – 67 years	EQ-5D-3L questionnaire	NA	Health state utility values were redacted, disutility values due to adverse events were published and have been used to inform the disutility values within the economic model	
NICE TA429[16]	Adult patients with CLL who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy Mean age: 71 years	EQ-5D-5L questionnaire	NA	Health state utility values were redacted, disutility values due to adverse events were published and have been used to inform the disutility values within the economic model	

EQ-5D – European quality-of-life five dimension; NICE – National Institute of Health and Care Excellence; NR – Not reported; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival; PRO – Patient reported outcomes; QALY – Quality-adjusted life-year; SD – Standard deviation

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B.3a.4.4 Age-related disutility

The base case included an age-related adjustment to account for the deterioration in HRQoL with age. The age-related adjustment was implemented using the methods descried in Ara and Brazier 2011 and applied to each cycle for the duration of the time horizon.[103] The utility decrements were estimated for all patients alive in each model cycle using the following equation:

$$HS_{utility} * (1 - (0.9508566 + 0.0212126 * (\%\, male) - 0.0002587 * age - 0.0000332 * age^2))$$

B.3a.4.5 Adverse reactions

The model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥1% of study subjects receiving treatment (across any BTKi treatment option). Events occurring in ≥1% of patients were considered appropriate to capture AEs that would impact patients in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. The Grade ≥3 AEs included in the model are reported in Table 79.

Within the base case, AEs in the model only have an impact on costs with AE-related costs applied to the proportion of patients experiencing the event in the first cycle of the model. A sensitivity analyses is explored which assessed the impact of AEs on HRQoL, with utility decrements applied to the proportion of patients experiencing the event in the first cycle of the model.

It is assumed that all AEs occur and are resolved in the first four weeks of treatment. In addition, only AEs associated with first-line treatment were considered, and AEs associated with subsequent lines were not considered.

Table 79: Grade ≥3 treatment-related AEs occurring in ≥1% of patients by treatment

Treatment	Zanubrutinib	Ibrutinib	Acalabrutinib
Anaemia	[redacted]	7.41%	6.70%
Thrombocytopenia		0.00%	2.79%
Pneumonia		11.85%	2.23%
Neutropenia		12.59%	11.17%
Hyponatremia		5.93%	0.00%
Hypertension		8.15%	3.91%
Febrile Neutropenia		0.00%	1.12%
Cataract		5.19%	0.00%
Atrial fibrillation		5.19%	3.91%
Source	SEQUOIA Cohort 1 and Cohort 2 CSR Table 39 and Table 14.3.1.2.4.1.1[75]	RESONATE 2 Burger 2020[120]	ELEVATE-TN Shaman 2020[79] and Shaman 2022[121]

AE – adverse event; CSR – clinical study report; TN – treatment naive.

In the sensitivity analysis assessing the impact of AEs on HRQoL, the model estimated the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates, the mean utility decrements associated with these AEs, and the mean duration of each AE episode. Utility decrements associated with AEs were sourced from previous NICE appraisals in CLL and published literature as the impact of AEs on HRQoL was not explicitly collected in the SEQUOIA study. The duration of AEs was derived from the same data sources wherever available. All AE utility decrements were applied in Cycle 1.

The utility decrements and duration estimates for AE used in the analysis are presented in Table 80.

Table 80: Utility decrements and duration estimates by AE

AE	Disutility	Source	Duration (days)	Source
Anaemia	-0.0900	TA487[59]	23.21	TA487[59]
Thrombocytopenia	-0.1100	TA487[59]	23.21	TA487[59]
Pneumonia	-0.1950	Tolley 2013[61]	18.20	TA359[58]
Neutropenia	-0.1630	TA487[59]	15.09	TA487[59]
Hyponatremia	-0.0200	Assumed the same as hypertension	21.00	Assumed the same as hypertension
Hypertension	-0.0200	Wehler 2018[62]	21.00	Assumption
Febrile Neutropenia	-0.1630	TA487[59]	15.09	TA487[59]
Cataract	-0.0900	Assumed the same as anaemia	23.21	Assumed the same as anaemia
Atrial fibrillation	-0.2200	Wehler 2018[62]	14	Assumption

AE – adverse event; TA – technology appraisal.

B.3a.4.6 Health-related quality of life data used in the cost-effectiveness analysis

As a CMA is being presented as the base-case analysis, the HRQoL impact is equalised across treatments and the impact on HRQoL is only considered in sensitivity analysis using a cost-utility approach.

As the utility values from SEQUOIA trial lacked face validity, published utility values identified within the SLR were used to inform the cost-utility scenario. In NICE TA689, a PF utility of 0.783 and PD utility of 0.6 were accepted. The PF utility of 0.783 was generated using EQ-5D for the age- and gender-matched general population as reported in Ara and Brazier (2011). The PD utility of 0.60 was informed by Holzner et al. (2004).[104] In Holzner et a. (2004), QoL was measured using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and the Functional Assessment of Cancer Therapy (FACIT): General questionnaire in 418 cancer patients, 81 of whom had CLL. The utility value of 0.60 has been accepted in a number of previous NICE appraisals in CLL. The utilities used in the cost-utility scenario analysis are presented in Table 81.

Table 81: Summary of utility values for the cost-utility scenario analysis

State	Utility value: mean (standard error)	95% CI	Sourced
PF	0.783 (0.0064)	0.770, 0.795	EQ-5D score for the age- and sex-matched general population, based on the ERG preferred value in NICE TA689[4]
PD	0.600 (0.0597)	0.481, 0.714	Holzer et al. 2004[104]

CI – Confidence interval; ERG – Evidence Review Group; EQ-5D – EuroQoL Five Dimensions; PD – Progressed disease; PF – Progression-free.

B.3a.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify studies reporting on the cost and resource use of patients with previously untreated CLL. Full details of the process and methods used to identify and select the cost and resource use data relevant to the technology being evaluated are presented in in Appendices I.

The SLR identified three cost and resource use studies from a UK perspective and two NICE appraisals for patients with previously untreated CLL.

Consistent with the studies identified in the SLR, the following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of primary and subsequent treatment
- Medical resource use costs
- The cost of unplanned events, such as AEs and terminal care costs.

For the cost inputs, an NHS and PSS perspective was adopted. Unit costs of drug acquisition, administration, resources use, and AE management were based on standard costing sources. The types and frequencies of resources associated with disease management, monitoring, and terminal care were derived based on previous NICE appraisals or consulted with clinical experts.

B.3a.5.1 Intervention and comparators' costs and resource use

B.3a.5.1.1 Drug acquisition costs

Drug acquisition costs were based on the dosing regimens presented in Table 82 and costs per pack and cycle are presented in Table 83. Dosing information was sourced from the respective SmPCs and costs were sourced from the BNF. In instances where multiple pack prices were available, the pack price with the lowest cost per mg was used. [redacted]

As discussed in Section B.3a.3.2.4 Treatment duration, primary treatment with BTKi is given until disease progression in the base case and scenario analyses were explored with alternative treatment duration assumptions. As discussed in Section B.3a.3 .3.2 PFS in 2L, subsequent treatment with venetoclax-rituximab is informed by PFS in 2L and capped such that patients did not receive more than the SmPC stated dose i.e. venetoclax for a maximum duration of 2 years and rituximab for a maximum duration of six 28-day cycles. All patients are modelled to receive subsequent treatment with venetoclax-rituximab at progression to align with the use of MURANO to inform PPS and duration of subsequent treatment.

Table 82: Dosing regimen of treatments included in the economic model

Treatment	Dosing regimen	Source
Zanubrutinib	320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or unacceptable toxicity	SEQUOIA trial[69]
Acalabrutinib	100 mg administered orally twice daily until PD or unacceptable toxicity	Acalabrutinib SmPC[107]
Ibrutinib	420 mg administered orally once daily until PD or unacceptable toxicity	Ibrutinib SmPC[106]
Venetoclax-rituximab *(Subsequent treatment only)*	Venetoclax: 20 mg once daily for 7 days, gradually increasing to 400mg over a period of 5 weeks. 400 mg administered orally once daily for a total of two years Rituximab: first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 IV on day one of each cycle for a maximum of six cycles	Venetoclax SmPC[111]

PD – Progressed disease; IV – Intravenous; SmPC – Summary of Product Characteristics.

The model considers wastage for IV drugs in the base case, for treatments that depend on body surface area (BSA), namely rituximab, as there is a potential that some of the drug will be wasted if perfect vial sharing is not practiced. A BSA of 1.92m^2 (SD: 0.20 m^2) was calculated from SEQUOIA. Relative dosing intensity is assumed at 100% for all treatments, aligned with the assumption accepted in NICE TA689.[4]

Table 83: Drug package price and cost per cycle

Treatment	Dosage strength	Pack size/vial volume	Administration route	Cost per pack (£)	Cost per cycle (£)
Zanubrutinib	80 mg	120	Oral	[redacted]	[redacted]
Acalabrutinib	100mg	60	Oral	5,059.00	4,721.73
Ibrutinib	420 mg	28	Oral	4,292.40	4,292.40
Venetoclax *(Subsequent treatment only)*	100mg	7	Oral	299.34	Cycle 1: 1,107.56 Cycles 2-26: 4,789.44
Rituximab *(Subsequent treatment only)*	10mg/ml 10mg/ml 120mg/ml	10ml 50ml 12ml	IV	157.17 785.84 1,344.65	Cycle 1: 1,198.56 Cycle 2-6: 1,339.28

IV – intravenous. Source: British National Formulary 2022.[122]

B.3a.5.1.2 Drug administration costs

Drug administration costs were applied to IV drugs with costs varying between initial and subsequent administrations. Medications that were orally administered did not incur administration costs. Unit costs for all categories of administration were based on National Schedule of NHS Costs and are presented in Table 84.[123]

Table 84: Drug administration costs

Description of cost	Use in model	Unit cost (£)	Source
Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance	Rituximab: one administration within Cycle 1	526.52	National Schedule of NHS Costs 2020/21[123]
Deliver Subsequent Elements of a Chemotherapy Cycle	Rituximab: one administration per cycle for Cycles 2-6	470.62	National Schedule of NHS Costs 2020/21[123]

NHS – National Health Service.

B.3a.5.2 Health-state unit costs and resource use

Costs related to routine follow-up and disease management included in the model were calculated through a micro-costing approach where resource use was multiplied by the unit cost for each resource item. Disease management costs are differentiated by health state (i.e., progression status) and are presented in Table 85.

The resource use data assigned to the PF and PD states were sourced from NICE TA689 for acalabrutinib and unit costs of medical resource were extracted from NHS National Schedule of Costs 2020/21.[4,123] The costs and resource use were validated at an advisory board conducted by the Company (03 November 2022). Clinical experts highlighted that transfusion burden was more specific to patients treated with CIT and so this cost was omitted from the disease management costs. Furthermore, it was noted that the use of chest x-rays had been largely replaced with radiological assessments (i.e., CT scans).[11]

Table 85: Medical resource unit costs and frequencies

Resource item	Costs		Resource use per cycle		
	Unit (£)	Source	PF state	PD state	Source
Full blood count	3.63	National Schedule of NHS Costs 2020/21[123]	0.31	0.61	NICE TA689[4]
Lactate dehydrogenase	1.85	National Schedule of NHS Costs 2020/21[123]	0.23	0	NICE TA689[4]
Haematologist visits	157.89	National Schedule of NHS Costs 2020/21[123]	0.15	0.46	NICE TA689[4]
CT scan	105.66	National Schedule of NHS Costs 2020/21[123]	0	0.15	NICE TA689[4] Clinical expert opinion
Bone marrow exam	574.44	National Schedule of NHS Costs 2020/21[123]	0	0.08	NICE TA689[4]
Inpatient visit (non-surgical)	750.17	National Schedule of NHS Costs 2020/21[123]	0	0.31	NICE TA689[4]
Aggregated cost per cycle			**£25.23**	**£369.20**	

CT – Computerised tomography; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PD – Progressed disease; PF – Progression-free.

B.3a.5.3 Adverse reaction unit costs and resource use

As described in Section B.3a.4.5 Adverse reactions, the model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥1% of study subjects receiving treatment (across any BTKi treatment option). Total AE costs were calculated as the product of the AE incidence, as presented in Table 79, and the respective unit cost as presented in Table 86. It is assumed that all AEs occur and are resolved in the first four weeks of treatment and only AEs associated with first-line treatment were considered.

Table 86: AE management costs

Adverse event	Cost (£)	Source	Comment
Anaemia	721.99	National Schedule of NHS Costs 2020/21[123]	SA09 Other Red Blood Cell Disorders with CC Score 0-5, non-elective short stay
Thrombocytopenia	881.88	National Schedule of NHS Costs 2020/21[123]	SA12 Thrombocytopenia, non-elective short stay
Pneumonia	782.27	National Schedule of NHS Costs 2020/21[123]	DZ11 Lobar, Atypical or Viral Pneumonia, non-elective short stay
Neutropenia	761.01	National Schedule of NHS Costs 2020/21[123]	SA35 Agranulocytosis, non-elective short stay
Hyponatremia	518.83	National Schedule of NHS Costs 2020/21[123]	KC04 Inborn Errors of Metabolism, score 0-2 non-elective short stay
Hypertension	537.86	National Schedule of NHS Costs 2020/21[123]	EB04Z Hypertension, non-elective short stay

Adverse event	Cost (£)	Source	Comment
Febrile Neutropenia	2,719.97	National Schedule of NHS Costs 2020/21[123]	SA35 Agranulocytosis, non-elective short stay and long stay
Cataract	1,821.35	National Schedule of NHS Costs 2020/21[123]	BZ32-BZ34, non-elective short stay and long stay
Atrial fibrillation	782.27	National Schedule of NHS Costs 2020/21[123]	Assume the same as infection (DZ11)

AE – Adverse event; CC – Complication and comorbidity; NHS – National Health Service.

B.3a.5.4 Miscellaneous unit costs and resource use

B.3a.5.4.1 Terminal care costs

Costs for terminal care are applied as a one-off cost to each death event in the model. The cost of end of life care was sourced from Round, Jones and Morris 2015, identified from the manufacturer submissions for NICE TA429, TA561 and TA689 and estimated the direct and indirect cost for lung, breast, colorectal and prostate patients at the end of life in England and Wales.[4,16,19,124] The terminal cost applied in the analysis is £7,000.72.

B.3a.5.4.2 TLS management costs

The model accounts for one-time monitoring costs for venetoclax at treatment initiation. These were included to account for the costs associated with laboratory tumour lysis syndrome (TLS) prophylaxis required for all patients before initiation of venetoclax treatment. The one-time costs for laboratory TLS prophylaxis were calculated based on the TLS risk distribution (i.e., stratified by low, intermediate, and high) and the estimated TLS prophylaxis cost per each risk category. TLS risk categories were obtained from MURANO and the TLS prophylaxis costs were sourced from the NICE TA561[19] (Table 87). The TLS management cost applied in the analysis is £1,950.08.

Table 87: TLS management costs

Risk category	Proportion	Cost (£)
Low	17.53%	1,430.40
Intermediate	54.64%	2,016.54
High	27.84%	2,146.81
Total		1,950.08
Source	Seymour 2018[125]	NICE TA561[19]

TLS – Tumour lysis syndrome.

B.3a.6 Severity

As a CMA is presented, the severity weight calculations were not considered relevant to this appraisal.

B.3a.7 Uncertainty

The key uncertainties in the economic evaluation relate to the immaturity of data. The long-term extrapolations are informed by less than half of the trial population and therefore are associated with uncertainty. Furthermore, the immaturity of data led to wide confidence intervals in the MAICs. However, the uncertainty in the MAIC results were alleviated in the cost-minimisation approach. In addition, the long-term extrapolations, assumptions on survival and estimates of comparative efficacy were validated with clinical, health economic and statistical experts at an advisory board (03 November 2022) held by the Company.[11]

Furthermore, the uncertainty in the model results were explored through extensive deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenario analyses. In the DSA, each variable was systematically increased and decreased based on 95% confidence intervals or published ranges. In the absence of data, the higher and lower values were calculated as ± 20% of the mean base-case value.

In the PSA, values were drawn at random for each variable from its uncertainty distribution. The model allowed the beta, gamma, log-normal, normal, and Dirichlet distributions to be used and also included Cholesky decomposition matrix calculation fields for modelling pairs of input parameters for which the covariance structure between two variables was known, such as for the survival curves (Table 88).

A number of scenario analyses were also performed to assess the impact of alternative assumptions and data sources which were not captured within the DSA and PSA.

Table 88: Distribution options by model parameter for PSA

Parameter	Distribution
Proportion of female	Beta distribution
Starting age, BSA (m^2), weight	Normal distribution
TTP, PrePS, TTD, PPS, PFS in 2L survival extrapolations	Normal distribution (Cholesky decomposition)
HRs of TTP	Log-normal distribution
Risk of experiencing AEs	Beta distribution
Subsequent treatment duration	Gamma distribution
Health state related utility	Beta distribution
Utility decrement due to AEs	Normal distribution
Duration of AE	Gamma distribution
Disease management and monitoring costs AE management costs Subsequent treatment costs	Gamma distribution

TLS prophylaxis treatment costs	
Proportion of patients by TLS related risk	Dirichlet distribution
Proportion of patients receiving subsequent treatment	Dirichlet distribution

AE – Adverse event; BSA – Body surface area; HR – Hazard ratio; PFS – Progression-free survival; PPS – Post-progression survival; PrePS – Pre-progression survival; TLS – Tumour lysis syndrome; TTD – Time to discontinuation; TTP – Time-to-progression; 2L – Second-line.

B.3a.8 Managed access proposal

A managed access proposal is not considered relevant for zanubrutinib for treating patients with previously untreated CLL.

B.3a.9 Summary of base-case analysis inputs and assumptions

B.3a.9.1 Summary of base-case analysis inputs

A summary of the key parameters used in the CMA is presented in Table 89.

Table 89: Summary of parameters used in the CMA

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model settings			
Population	Pooled (SEQUOIA arm A and arm C)	N/A	B.3a.2 Economic analysis
Perspective	Payer (UK NHS and PPS)	N/A	
Time horizon	Lifetime (30 years)	Fixed	
Proportion females	[redacted]	95% CI (0.290, 0.388) Beta	
Starting age in model (years)	[redacted]	SE: 0.42 (Normal)	
Weight (kg)	[redacted]	SE: 0.86 (Normal)	
Body surface area (m^2)	1.92	SE: 0.01 (Normal)	
Half-cycle correction	Yes	Fixed	
Discount rate (cost and outcomes)	3.5%	Fixed	
Clinical parameters			
Efficacy			
TTP distribution for zanubrutinib (pooled population)	Generalised gamma	N/A	B.3a.3 Clinical parameters and variables
PrePS distribution for all treatments (pooled population)	Generalised gamma		

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Treatment duration for BTKis	Treat until disease progression		
PPS – data source	MURANO		
PPS – distribution	Exponential		
PFS in 2L – data source	MURANO		
PFS in 2L – distribution	Gompertz		
Hazard ratio			
Zanubrutinib versus acalabrutinib	1.00	Fixed	-
Zanubrutinib versus ibrutinib	1.00	Fixed	-
Probability of AE – zanubrutinib			
Anaemia	[redacted]	Sample size (351) used to model variance around the mean (Beta)	B.3a.3 Clinical parameters and variables
Thrombocytopenia	[redacted]		
Pneumonia	[redacted]		
Neutropenia	[redacted]		
Hyponatremia	[redacted]		
Hypertension	[redacted]		
Febrile Neutropenia	[redacted]		
Cataract	[redacted]		
Atrial fibrillation	[redacted]		
Probability of AE – ibrutinib			
Anaemia	0.0741	Sample size (135) used to model variance around the mean (Beta)	B.3a.3 Clinical parameters and variables
Thrombocytopenia	0.0000		
Pneumonia	0.1185		
Neutropenia	0.1259		
Hyponatremia	0.0593		
Hypertension	0.0815		
Febrile Neutropenia	0.0000		
Cataract	0.0519		
Atrial fibrillation	0.0519		
Probability of AE – acalabrutinib			
Anaemia	0.0670	Sample size (179) used to model variance around the mean (Beta)	B.3a.3 Clinical parameters and variables
Thrombocytopenia	0.0279		
Pneumonia	0.0223		
Neutropenia	0.1117		
Hyponatremia	0.0000		
Hypertension	0.0391		
Febrile Neutropenia	0.0112		
Cataract	0.0000		
Atrial fibrillation	0.0391		
Duration of adverse event (days)			

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Anaemia	23.21	SE: 4.64 (Gamma)	B.3a.4 Measurement and valuation of health effects
Thrombocytopenia	23.21	SE: 4.64 (Gamma)	
Pneumonia	18.20	SE: 3.64 (Gamma)	
Neutropenia	15.09	SE: 3.02 (Gamma)	
Hyponatremia	21.00	SE: 4.20 (Gamma)	
Hypertension	21.00	SE: 4.20 (Gamma)	
Febrile Neutropenia	15.09	SE: 3.02 (Gamma)	
Cataract	23.21	SE: 4.64 (Gamma)	
Atrial fibrillation	14.00	SE: 2.80 (Gamma)	
Health-related quality of life parameters (scenario only)			
Health state utilities			
PFS	0.7830	SE: 0.0064 (Beta)	B.3a.4 Measurement and valuation of health effects
PD	0.6000	SE: 0.0597 (Beta)	
Disutilities			
Anaemia	-0.0900	SE: 0.0180 (Beta)	B.3a.4 Measurement and valuation of health effects
Thrombocytopenia	-0.1100	SE: 0.0220 (Beta)	
Pneumonia	-0.1950	SE: 0.0390 (Beta)	
Neutropenia	-0.1630	SE: 0.0326 (Beta)	
Hyponatremia	-0.0200	SE: 0.0040 (Beta)	
Hypertension	-0.0200	SE: 0.0040 (Beta)	
Febrile Neutropenia	-0.1630	SE: 0.0326 (Beta)	
Cataract	-0.0900	SE: 0.0180 (Beta)	
Atrial fibrillation	-0.2200	SE: 0.0440 (Beta)	
Cost parameters			
Disease management resource use			
PF: Full blood count	0.31	SE: 0.06 (Gamma)	B.3a.5 Cost and healthcare resource use identification
PF: LDH	0.23	SE: 0.05 (Gamma)	
PF: Haematologist visits	0.15	SE: 0.03 (Gamma)	
PD: Full blood count	0.61	SE: 0.12 (Gamma)	
PD: LDH	0.00	SE: 0.00 (Gamma)	
PD: Haematologist visits	0.46	SE: 0.09 (Gamma)	
PD: CT scan	0.15	SE: 0.03 (Gamma)	
PD: Bone marrow exam	0.08	SE: 0.02 (Gamma)	
PD: Inpatient visit (non-surgical)	0.31	SE: 0.06 (Gamma)	
Disease management costs			
Full blood count	£3.63	SE: £0.73 (Gamma)	B.3a.5 Cost and healthcare
LDH	£1.85	SE: £0.37 (Gamma)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Haematologist visits	£157.89	SE: £31.58 (Gamma)	resource use identification
CT scan	£105.66	SE: £21.13 (Gamma)	
Bone marrow exam	£574.44	SE: £114.89 (Gamma)	
Inpatient visit (non-surgical)	£750.17	SE: £150.03 (Gamma)	
End-of-life costs			
Terminal care	£7,000.72	SE: £1,400.14 (Gamma)	B.3a.5 Cost and healthcare resource use identification
TLS management resource us			
Proportion of patients: Low	17.53%	SE: 3.51% (Dirichlet)	B.3a.5 Cost and healthcare resource use identification
Proportion of patients: Intermediate	54.64%	SE: 10.93% (Dirichlet)	
Proportion of patients: High	27.84%	SE: 5.57% (Dirichlet)	
TLS management costs			
Low	£1,430.40	SE: £286.08 (Gamma)	B.3a.5 Cost and healthcare resource use identification
Intermediate	£2,016.54	SE: £403.31 (Gamma)	
High	£2,146.81	SE: £429.36 (Gamma)	
Adverse event costs			
Anaemia	£721.99	SE: £125.97 (Gamma)	B.3a.5 Cost and healthcare resource use identification
Thrombocytopenia	£881.88	SE: £160.93 (Gamma)	
Pneumonia	£782.27	SE: £381.63 (Gamma)	
Neutropenia	£761.01	SE: £141.16 (Gamma)	
Hyponatremia	£518.83	SE: £80.77 (Gamma)	
Hypertension	£537.86	SE: £193.48 (Gamma)	
Febrile Neutropenia	£2,719.97	SE: £357.12 (Gamma)	
Cataract	£1,821.35	SE: £143.76 (Gamma)	
Atrial fibrillation	£782.27	SE: £381.63 (Gamma)	
Treatment acquisition costs			
Zanubrutinib cost per pack	[redacted]	Fixed	B.3a.5 Cost and healthcare resource use identification
Ibrutinib cost per pack	£4,292.40	Fixed	
Acalabrutinib cost per pack	£5,059.00	Fixed	
Venetoclax cost per pack (subsequent treatment)	£299.34	Fixed	
Rituximab cost per pack (subsequent treatment)	10 ml vial: £157.17 50ml vial: £785.84 12ml vial: £1,344.65	Fixed	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Treatment administration costs			
Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£526.52	SE: £53.72 (Gamma)	B.3a.5 Cost and healthcare resource use identification
Subsequent Elements of a Chemotherapy Cycle	£470.62	SE: £48.02 (Gamma)	
Distribution of subsequent treatment			
Venetoclax-rituximab	100%	Fixed	B.3a.5 Cost and healthcare resource use identification

AE – Adverse event; CT – Computerised tomography; LDH – Lactate dehydrogenase; PD – Progressed disease; PFS – Progression-free survival; PPS – Post-progression survival; PrePS – Pre-progression survival; SE – Standard error; TTP – Time to treatment progression; TTD – Time to discontinuation.

B.3a.9.2 Assumptions

The key assumptions made in the model base case are presented in Table 90

Table 90: Key assumptions in the model

Model input	Assumption	Rationale
Time horizon	Lifetime	In line with NICE guidance[112] (assumed a 30-year life time horizon based on the age of the patient population in the SEQUOIA trial).
Equal efficacy between zanubrutinib and alternative BTKis	A cost-minimisation analysis is used, assuming non-inferiority between zanubrutinib, acalabrutinib and ibrutinib.	As discussed in Section B.3a.3.4 Relative efficacy, zanubrutinib is non-inferior to i) acalabrutinib in patients with both with previously untreated CLL who are unsuitable for FCR and BR therapy, both with and without 'high-risk' factors and ii) ibrutinib in patients in the 'high-risk' factors. Due to the wide confidence intervals produced in the MAIC, a cost-minimisation analysis was considered appropriate. This assumption was validated with clinical experts.
Aligned TTP and PrePS survival distributions	Generalised gamma	As PFS is comprised of TTP and PrePS, a decision was made to align the distributions used to extrapolate TTP and PrePS to provide a better representation of PFS. Equal TPP and PrePS was assumed across the three BTKis.
PPS data source for BTKis	MURANO OS data was used to inform PPS in the model for BTKis	Patients progressing on a BTKi, would typically be ineligible for a BTKi in the second line. UK clinicians have indicated there is a preference for treating with a BTKi prior to treating with VR.

Treatment duration	All patients treated with BTKis are assumed to be treated until progression	As per the respective SmPCs, patients are treated until progression meaning that treatment duration is informed by PFS in the model.
Treatment administration costs	No administration costs for BTKis	Regimens administered orally can be taken by patients at home. It is assumed that no costs are incurred.
Subsequent treatment costs	100% of patients are assumed to receive VR as a subsequent treatment upon progression	To align with the use of MURANO to inform PPS and PFS in second-line and reflect UK clinical practice.
Disease management and monitoring	Disease management and monitoring costs are assumed equal across treatment arms	It is assumed that monitoring of patients and associated costs will not vary across treatment arms.

BTK – Bruton tyrosine kinase; MAIC – Matching-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; PD – Progressed disease; PFS – Progression-free survival; PPS – Post-progression survival; PrePS – Pre-progression survival; SmPC – Summary of product characteristic; TTP – Time to treatment progression; VR – Venetoclax-rituximab.

B.3a.10 Base-case results

B.3a.10.1 Base-case cost-minimisation analysis results

The base-case results for the pooled SEQUOIA arm A and arm C population are presented in Table 91. Over a lifetime time horizon, treatment with zanubrutinib in patients with previously untreated CLL was associated with cost-savings of [redacted] and [redacted] per person, compared to ibrutinib and acalabrutinib, respectively.

Disaggregated results from the base-case analysis are presented in Appendix J.

Table 91: Base-case deterministic results in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

LYG – Life years gained; QALYs – Quality-adjusted life years.

B.3a.11 Exploring uncertainty

B.3a.11.1 Probabilistic sensitivity analysis

PSA was conducted in order to assess the impact of parameter uncertainty on the results of the analysis in the model base case; 1,000 simulations were performed, and for each simulation, a value was drawn at random for each variable from its uncertainty distribution simultaneously, and the resulting costs, outcomes, and incremental results were recorded.

The results of the base-case PSA are presented in Table 92 below and the total cost and QALY scatterplot is presented in Figure 54. Based on the PSA, treatment with zanubrutinib in patients with previously untreated CLL was associated with cost-savings of [redacted] and [redacted], for ibrutinib and acalabrutinib, respectively. The mean probabilistic results lie close to the deterministic results, indicating that the model is robust to parameter uncertainty.

Table 92: Base-case PSA results in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

LYG – Life years gained; PSA – Probabilistic sensitivity analysis; QALY – Quality-adjusted life year.

Figure 54: Total cost and QALY scatterplot for zanubrutinib vs ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

CLL – Chronic lymphocytic leukaemia; QALY – Quality-adjusted life year

B.3a.11.2 Deterministic sensitivity analysis

DSA was performed to explore the effect of uncertainty associated with varying individual model inputs or groups of individual model inputs. The results of the DSA are summarised in Table 93 and Figure 55 for ibrutinib and Table 94 and Figure 56 for acalabrutinib. The most influential factors on the DSA were the survival coefficients for the generalised gamma TTP curve in both the comparisons with ibrutinib and acalabrutinib.

Table 93: DSA results (incremental costs) for zanubrutinib vs ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Generalised Gamma model to project TTP for Zanubrutinib	[redacted]	[redacted]
Shape for Generalised Gamma model to project TTP for Zanubrutinib	[redacted]	[redacted]
Starting age	[redacted]	[redacted]
Shape for Generalised Gamma model to project pre-progression survival for All treatments	[redacted]	[redacted]
Proportion female	[redacted]	[redacted]
Scale for Generalised Gamma model to project TTP for Zanubrutinib	[redacted]	[redacted]
Cost of AEs per cycle with Ibrutinib	[redacted]	[redacted]
Intercept for Generalised Gamma model to project pre-progression survival for All treatments	[redacted]	[redacted]
Cost of AEs per cycle with Zanubrutinib	[redacted]	[redacted]

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; TPP – Time-to-progression.

Table 94: DSA results (incremental costs) for zanubrutinib vs acalabrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Generalised Gamma model to project TTP for Zanubrutinib	[redacted]	[redacted]
Shape for Generalised Gamma model to project TTP for Zanubrutinib	[redacted]	[redacted]
Starting age	[redacted]	[redacted]
Shape for Generalised Gamma model to project pre-progression survival for All treatments	[redacted]	[redacted]
Proportion female	[redacted]	[redacted]
Scale for Generalised Gamma model to project TTP for Zanubrutinib	[redacted]	[redacted]
Intercept for Generalised Gamma model to project pre-progression survival for All treatments	[redacted]	[redacted]
Cost of AEs per cycle with Acalabrutinib	[redacted]	[redacted]
Cost of AEs per cycle with Zanubrutinib	[redacted]	[redacted]

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; TPP – Time-to-progression.

Figure 55: Tornado plot of DSA results (incremental costs) for zanubrutinib vs ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; TPP – Time-to-progression.

Figure 56: Tornado plot of DSA results (incremental costs) for zanubrutinib vs acalabrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; TPP – Time-to-progression.

B.3a.11.3 Scenario analysis

Details of each of the included scenario analyses are presented in Table 95. Deterministic and probabilistic scenario analysis results for zanubrutinib versus both ibrutinib and acalabrutinib are presented in Table 96 and Table 97 below, respectively. The probabilistic results lie close to the deterministic results, indicating the robustness of the analyses to parameter uncertainty.

Table 95: Summary of scenario analyses

Base-case	Scenario analysis	Scenario analysis description
3.5% discount rate	No discounting	0% discount is assumed for costs to assess the impact of discounting
3.5% discount rate	High discount rates (6%)	6% discount is assumed for costs to assess the impact of discounting
TTP endpoint (IRC)	TTP endpoint (INV)	INV TTP is used to assess the impact on survival estimates
TTP/PrePS curve for zanubrutinib (Generalised gamma)	TTP/PrePS curve for zanubrutinib (Log-normal)	Log-normal distribution modelled for SEQUOIA TTP and PrePS
	TTP/PrePS curve for zanubrutinib (exponential)	Exponential normal distribution modelled for SEQUOIA TTP and PrePS
Treatment until progression	Use TTD data for zanubrutinib	SEQUOIA TTD data extrapolated and model for zanubrutinib time on treatment
PPS curve for BTKi (Exponential)	PPS curve for BTKi (Weibull)	Weibull distribution modelled for MURANP PPS
2L PFS curve for BTKi (Gompertz)	2L PFS curve for BTKi (Gen. Gamma)	Generalised gamma distribution modelled for MURANO 2L PFS
	2L PFS curve for BTKi (Weibull)	Weibull gamma distribution modelled for MURANO 2L PFS
Include wastage	Exclude wastage	Wastage for IV treatments is excluded in the analysis
Include AE costs	Exclude AE costs	The impact of AEs on total costs is excluded from the analyses
Exclude AE impact to QALYs	Apply AE impact to QALYs	The impact of AEs on QALYs is included in the analysis
Pooled data (cost-min)	Unfit data (cost-min)	A cost-minimisation analysis utilising the SEQUOIA Cohort 1, arm A data for TPP and PrePS
	High-risk data (cost-min)	A cost-minimisation analysis utilising the SEQUOIA Cohort 2, arm C data for TPP and PrePS

Base-case	Scenario analysis	Scenario analysis description
	Pooled (cost-utility - ELEVATE-TN MAIC model 1)	A cost-utility analysis utilising the pooled SEQUOIA arm A and arm C data for TPP and PrePS and the MAIC Model 1 versus acalabrutinib
	Pooled (cost-utility - ELEVATE-TN MAIC model 2)	A cost-utility analysis utilising the pooled SEQUOIA arm A and arm C data for TPP and PrePS and the MAIC Model 2 versus acalabrutinib
	Unfit data (cost-utility - ELEVATE-TN MAIC model 1)	A cost-utility analysis utilising the SEQUOIA Cohort 1, arm A data for TPP and PrePS and the MAIC Model 1 versus acalabrutinib
	Unfit data (cost-utility - ELEVATE-TN MAIC model 2)	A cost-utility analysis utilising the SEQUOIA Cohort 1, arm A data for TPP and PrePS and the MAIC Model 2 versus acalabrutinib
	High-risk data (cost-utility - ELEVATE-TN MAIC model 1)	A cost-utility analysis utilising the SEQUOIA Cohort 2, arm C data for TPP and PrePS and the MAIC Model 1 versus acalabrutinib
	High-risk data (cost-utility - ELEVATE-TN MAIC model 2)	A cost-utility analysis utilising the SEQUOIA Cohort 2, arm C data for TPP and PrePS and the MAIC Model 2 versus acalabrutinib
	High-risk data (cost-utility – R/R as proxy)	A cost-utility analysis utilising the SEQUOIA Cohort 2, arm C data for TPP and PrePS and the R/R HR 'high-risk' as a proxy versus ibrutinib from ALPINE and acalabrutinib using the ELEVATE-RR MAIC
	High-risk data (cost-utility – naïve comparison based on Mato et al.)	A cost-utility analysis utilising the SEQUOIA Cohort 2, arm C data for TPP and PrePS and the naïve comparison versus ibrutinib using Mato et al. data

AE – Adverse event; BTKi – Bruton tyrosine kinase inhibitor; INV – Investigator; MAIC – Matching-adjusted indirect comparison; min – Minimisation; PrePS – Pre-progression survival; PFS – Progression-free survival; PPS – Post-progression survival; RR – Relapsed/refractory; TTD – Time to treatment discontinuation; TTP – Time-to-progression; R/R – Relapsed/refractory; 2L – Second-line

Table 96: Summary of scenario analyses results for zanubrutinib vs ibrutinib and acalabrutinib – deterministic

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base-Case	[redacted]	-	-	-	[redacted]	-	-	-
No Discounting	[redacted]	-	-	-	[redacted]	-	-	-
High Discount rates (6%)	[redacted]	-	-	-	[redacted]	-	-	-
TTP endpoint (INV)	[redacted]	-	-	-	[redacted]	-	-	-
TTP/PrePS curve for zanubrutinib (Log-normal)	[redacted]	-	-	-	[redacted]	-	-	-
TTP/PrePS curve for zanubrutinib (exponential)	[redacted]	-	-	-	[redacted]	-	-	-
Use TTD data for zanubrutinib	[redacted]	-	-	-	[redacted]	-	-	-
PPS curve for BTKi (Weibull)	[redacted]	-	-	-	[redacted]	-	-	-
2L PFS curve for BTKi (Generalised Gamma)	[redacted]	-	-	-	[redacted]	-	-	-
2L PFS curve for BTKi (Weibull)	[redacted]	-	-	-	[redacted]	-	-	-
Exclude wastage	[redacted]	-	-	-	[redacted]	-	-	-
Exclude AE costs	[redacted]	-	-	-	[redacted]	-	-	-
Apply AE impact to QALYs (cost-utility)	[redacted]	-	0.0018	Dominant	[redacted]	-	0.0005	Dominant
Unfit data (cost-min)	[redacted]	-	-	-	[redacted]	-	-	-
High-risk data (cost-min)	[redacted]	-	-	-	[redacted]	-	-	-

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pooled (cost-utility - ELEVATE-TN MAIC model 1)	-	-	-	-	[redacted]	0.0105	0.0562	Dominant
Pooled (cost-utility - ELEVATE-TN MAIC model 2)	-	-	-	-	[redacted]	0.0027	0.0147	Dominant
Unfit data (cost-utility - ELEVATE-TN MAIC model 1)	-	-	-	-	[redacted]	0.0057	0.0588	Dominant
Unfit data (cost-utility - ELEVATE-TN MAIC model 2)	-	-	-	-	[redacted]	0.0014	0.0156	Dominant
High-risk data (cost-utility - ELEVATE-TN MAIC model 1)	-	-	-	-	[redacted]	0.0113	0.0470	Dominant
High-risk data (cost-utility - ELEVATE-TN MAIC model 2)	-	-	-	-	[redacted]	0.0029	0.0119	Dominant
High-risk data (cost-utility – R/R as proxy)	[redacted]	0.0766	0.3108	Dominant	[redacted]	0.0519	0.2120	Dominant
High-risk data (cost-utility – naïve comparison based on Mato et al.)	[redacted]	0.0458	0.1888	Dominant	-	-	-	-

AE – Adverse event; BTKi – Bruton tyrosine kinase inhibitor; ICER – Incremental cost-effectiveness ratio; INV – Investigator; LYG – Life years gained; MAIC – Matching-adjusted indirect comparison; min – Minimisation; N/A – not applicable; PrePS – Pre-progression survival; PFS – Progression-free survival; PPS – Post-progression survival; QALYs – Quality-adjusted life year; RR – Relapsed/refractory; TTD – Time to treatment discontinuation; TTP – Time-to-progression; R/R – Relapsed/refractory; 2L – Second-line.

Table 97: Summary of scenario analysis results for zanubrutinib vs ibrutinib and acalabrutinib – probabilistic (n=1,000 iterations)

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base-Case	[redacted]	-	-	-	[redacted]	-	-	-
No Discounting	[redacted]	-	-	-	[redacted]	-	-	-
High Discount rates (6%)	[redacted]	-	-	-	[redacted]	-	-	-
TTP endpoint (INV)	[redacted]	-	-	-	[redacted]	-	-	-
TTP/PrePS curve for zanubrutinib (Log-normal)	[redacted]	-	-	-	[redacted]	-	-	-
TTP/PrePS curve for zanubrutinib (exponential)	[redacted]	-	-	-	[redacted]	-	-	-
Use TTD data for zanubrutinib	[redacted]	-	-	-	[redacted]	-	-	-
PPS curve for BTKi (Weibull)	[redacted]	-	-	-	[redacted]	-	-	-
2L PFS curve for BTKi (Generalised Gamma)	[redacted]	-	-	-	[redacted]	-	-	-
2L PFS curve for BTKi (Weibull)	[redacted]	-	-	-	[redacted]	-	-	-
Exclude wastage	[redacted]	-	-	-	[redacted]	-	-	-
Exclude AE costs	[redacted]	-	-	-	[redacted]	-	-	-
Apply AE impact to QALYs	[redacted]	-	0.0018	Dominant	[redacted]	-	0.0005	Dominant
Unfit data (cost-min)	[redacted]	-	-	-	[redacted]	-	-	-
High-risk data (cost-min)	[redacted]	-	-	-	[redacted]	-	-	-

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pooled (cost-utility - ELEVATE-TN MAIC model 1)	-	-	-	-	[redacted]	0.0251	0.0571	Dominant
Pooled (cost-utility - ELEVATE-TN MAIC model 2)	-	-	-	-	[redacted]	0.0065	0.0119	Dominant
Unfit data (cost-utility - ELEVATE-TN MAIC model 1)	-	-	-	-	[redacted]	0.0203	0.0432	Dominant
Unfit data (cost-utility - ELEVATE-TN MAIC model 2)	-	-	-	-	[redacted]	0.0041	0.0027	Dominant
High-risk data (cost-utility - ELEVATE-TN MAIC model 1)	-	-	-	-	[redacted]	0.0310	0.0631	Dominant
High-risk data (cost-utility - ELEVATE-TN MAIC model 2)	-	-	-	-	[redacted]	0.0042	0.0072	Dominant
High-risk data (cost-utility – R/R as proxy)	[redacted]	0.1765	0.3874	Dominant	[redacted]	0.1162	0.2552	Dominant
High-risk data (cost-utility – naïve comparison based on Mato et al.)	[redacted]	0.1014	0.2266	Dominant	-	-	-	-

AE – Adverse event; BTKi – Bruton tyrosine kinase inhibitor; ICER – Incremental cost-effectiveness ratio; INV – Investigator; LYG – Life years gained; MAIC – Matching-adjusted indirect comparison; min – Minimisation; PrePS – Pre-progression survival; PFS – Progression-free survival; PPS – Post-progression survival; QALYs – Quality-adjusted life year; RR – Relapsed/refractory; TTD – Time to treatment discontinuation; TTP – Time-to-progression; R/R – Relapsed/refractory; 2L – Second-line.

B.3a.12 Subgroup analysis

The base case utilised pooled data from SEQUOIA arm A and arm C, which reflects the full cohort of 'unfit' and 'high-risk' previously untreated patients with CLL. Scenario analyses were conducted using data from SEQUOIA arm A in the 'unfit' population and arm C in the 'high-risk' population with details of the extrapolations and curve selection presented in Appendix M. Results from these scenarios are presented in Section B.3a.11.3 Scenario analysis.

In a comparison with acalabrutinib using data from SEQUOIA arm A to mirror the 'unfit' population, zanubrutinib was associated with a cost saving of £[redacted]. In a further scenario analysis using a cost-utility approach in the 'unfit' population, zanubrutinib was demonstrated to be less costly (£[redacted]) and more efficacious ([redacted] QALY gain) and so dominated acalabrutinib. Probabilistic scenario analyses results lay close to the deterministic results for these subgroup analyses.

In a comparison with acalabrutinib and ibrutinib using data from SEQUOIA arm C to mirror the 'high-risk' population, zanubrutinib was associated with a cost saving of £[redacted] compared to acalabrutinib and £[redacted] compared to ibrutinib. In further scenario analyses using a cost-utility approach in the 'high-risk' population, zanubrutinib dominated both acalabrutinib (£[redacted] cost saving; [redacted] QALY gain) and ibrutinib (£[redacted] cost saving; 0.3108 QALY gain) when using R/R data as a proxy. In a further scenario analysis using the results from the naïve comparison versus ibrutinib using Mato et al. data, zanubrutinib also dominated ibrutinib (£[redacted] cost saving; 0.1888 QALY gain). Probabilistic sensitivity analyses results lay close to the deterministic results for these subgroup analyses.

B.3a.13 Benefits not captured in the QALY calculation

Whilst the impact of AEs on HRQoL are not modelled in the model base case, reduced inhibition of off-target kinases with zanubrutinib might lead to reduced risk of cardiac AEs and tolerability issues observed with ibrutinib and acalabrutinib leading to discontinuation of treatment, which is not captured in the model. Results at a median follow up time of 12 months from an ongoing, phase 2, single-arm trial evaluating the efficacy of zanubrutinib in patients previously treated for B-cell malignancies who became intolerant to ibrutinib, acalabrutinib, or both, demonstrated that the majority of intolerance events (70% for ibrutinib and 83% for acalabrutinib) did not recur with zanubrutinib, and that no events recurred with higher severity.[59] Furthermore, AEs associated with zanubrutinib seemed more tolerable and manageable for patients than those associated with other BTK inhibitors.[59] This suggests

that zanubrutinib might offer safety and tolerability advantages over existing BTKis which is not captured in the model.

B.3a.14 Validation

Upon completion of the model programming, a rigorous and comprehensive quality check of the model was conducted by an internal health economist not involved with the original programming to ensure the completed model contained no errors and worked as intended. This included validating the logical structure of the model, the expressions and sequences of calculations, and the values of numbers supplied as model inputs.

An extreme-value sensitivity analysis was also conducted on all applicable model inputs. Whilst conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the results included in this report.

Furthermore, the model structure, assumptions, model inputs and outputs were validated by UK clinical experts and economic in attendance at an advisory board (03 November 2022) organised by the Company, and feedback from the experts was incorporated into this submission.[11] In particular, the survival extrapolations, choice of comparators and assumption of non-inferiority between zanubrutinib and acalabrutinib and ibrutinib, respectively, were validated at the advisory board. A review of treatments for CLL in previous NICE TAs and published literature was carried out to further validate the key model assumptions, inputs and outputs.

The modelled survival outputs were also validated against long-term published data in patients with previously untreated CLL from the ELEATE-TN and RESONATE-2 trials. As can be seen in Table 98, the outputs for PFS and OS for the three BTKis under the non-inferiority assumption closely align to the clinical trial data, increasing the validity of the results.

Table 98: Comparison of modelled PFS and OS versus published clinical trial data in previously untreated CLL

Dataset	Proportion of patients at 1 year	Proportion of patients at 5 years	Proportion of patients at 8 years
PFS			
Modelled BTKis	93%	68%	56%
RESONATE-2 ibrutinib arm[109]	94%	67%	60%
ELEVATE-TN acalabrutinib arm[121]	96%	NR	NR
OS*			
Modelled BTKis	97%	87%	79%
RESONATE-2 ibrutinib arm[109]	97%	83%	NR

*Long-term OS not available from ELEVATE-TN. BTKi – Bruton tyrosine kinase inhibitor; CLL – Chronic lymphocytic leukaemia; NR – Not reached; OS – Overall survival; PFS – Progression-free survival.

B.3a.15 Interpretation and conclusions of economic evidence

B.3a.15.1 Summary

A 3-health state semi-Markov model was developed to evaluate the cost saving of zanubrutinib versus relevant comparators in patients with previously untreated CLL:

- Acalabrutinib in patients with previously untreated 'unfit' and ''high-risk' CLL, aligned with the recommendations made by NICE in TA689.[4]
- Ibrutinib in patients with previously untreated 'high-risk' CLL, aligned with the recommendations made by NICE in TA429.[16]

The model structure was chosen to model patients' survival outcomes in the 3-health states (PF and PD, and death) as it allowed for more granular disease modelling and event rates to be captured in the model. TTP and PrePS was informed from SEQUOIA extrapolated trial data and published data sourced were used to inform extrapolated post-progression outcomes (PPS and PFS in 2L), as data from SEQUOIA was considered too immature at the latest data cut-off of 07 March 2022. For the base-case, a non-inferiority assumption of equalised efficacy was assumed across all three BTKi, based on results from multiple MAICs and clinical expert opinion. Sensitivity analyses in the form of cost-utility analyses were conducted to relax this non-inferiority assumption.

Clinical data were primarily sourced from the pivotal trial for zanubrutinib in patients with previously untreated CLL, SEQUOIA. To align with the anticipated treatment pathway, as indicated by BSH guidelines and UK clinical expert opinion, published OS and PFS data for venetoclax-rituximab in the second-line setting from the MURANO study was used to inform

the transition of patients post-progression. Safety data were sourced from SEQUOIA and key comparator clinical trials (ELEVATE-TN and RESONATE-2).

The model included treatment cost categories relevant to a UK NHS and PPS perspective, with costs and resource input sourced from appropriate UK based sources. Utilities were considered in sensitivity analysis using a cost-utility approach, with utility data sourced from published literature aligned with NICE/EAG preferred assumptions in NICE TA689.[4]

Overall, the results of the economic analysis are considered generalisable to UK clinical practice.

B.3a.15.2 Summary of cost-minimisation estimates

In the base-case analysis, the CMA demonstrated that treatment with zanubrutinib is associated with cost savings of [redacted] versus acalabrutinib ('unfit' and 'high-risk' populations) and [redacted] versus ibrutinib ('high-risk' population) in patients with previously untreated CLL.

Results from the OWSA indicated that the analysis was most sensitive to survival coefficients for the generalised gamma TTP curve.

Probabilistic results over 1,000 iterations lay close to the deterministic results for the base case and all scenarios conducted, indicating that the model was robust to parameter uncertainty. Across all scenario analyses conducted, zanubrutinib remained cost saving compared to acalabrutinib and ibrutinib. Cost-utility analyses (across the pooled, 'unfit' and 'high-risk populations') conducted to explore the impact of relaxing the non-inferiority assumptions indicated that zanubrutinib was more effective and less costly than both acalabrutinib and ibrutinib, and hence dominated both treatment alternatives (both deterministically and probabilistically).

B.3b Cost-effectiveness: R/R CLL

B.3b.1 Published cost-effectiveness studies

An SLR was conducted to identify studies reporting the cost-effectiveness, HRQoL and cost and resource use of patients with R/R CLL. Full details of the process and methods used to identify and select the economic evidence relevant to the technology being evaluated are presented in in Appendices G-H. A summary of these studies is provided in Table 66 in Section B.3a.1 Published cost-effectiveness studies.

B.3b.2 Economic analysis

The SLR did not identify any previous economic evaluations of zanubrutinib in patients with R/R CLL.

As discussed in Section B.2.9 Indirect and mixed treatment comparisons , two MAIC analyses were conducted which demonstrated that zanubrutinib is at least non-inferior to acalabrutinib in patients with R/R CLL. UK clinical experts validated this conclusion at an advisory board (03 November 2022) organised by the Company.[11]

Furthermore, as presented in Section B.2b.6 Clinical effectiveness results of the relevant studies: R/R CLL, the ALPINE trial met its primary endpoint, with zanubrutinib demonstrating a statistically significant improvement in ORR determined by INV-assessment compared to ibrutinib in patients with R/R CLL. Clinical superiority of zanubrutinib over ibrutinib was supported by consistently improved outcomes in key secondary endpoints, with a statistically significant improvement in INV-assessed and IRC-assessed PFS demonstrated. It is therefore clinically plausible to conclude that zanubrutinib will be at least non-inferior to ibrutinib in patients with R/R CLL. This conclusion is conservative given that late breaking data has confirmed that after a median follow-up of 29.6 months, zanubrutinib continued to demonstrate a statistically significant improvement in PFS compared to ibrutinib.[77] Furthermore, median PFS was not reached in the zanubrutinib group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group, highlighting the significant improvement in PFS in patients treated with zanubrutinib compared to ibrutinib.[77]

To reflect these findings, a CMA was developed in Microsoft® Excel to estimate the incremental costs of zanubrutinib versus both acalabrutinib and ibrutinib for patients with R/R CLL.

The SLR identified one economic evaluation utilising a CMA approach. In TA689, a PSM model structure was used to compare acalabrutinib versus ibrutinib within a CMA.[4] To align with the past precedence CMA being accepted by NICE, a PSM structure was utilised to compare zanubrutinib with acalabrutinib and with ibrutinib in patients with R/R CLL. The choice of model structure was validated by clinical and economic experts in attendance at an advisory board (03 November 2022) held by the Company, with the model structure deemed suitable for the decision problem.[11]

Key characteristics of the CMA are presented in Table 99 and compared against the characteristics of previous economic evaluations submitted to NICE for BTKi treatment in patients with R/R CLL.

Table 99: Features of the economic analysis

Factor	Previous evaluations for BTKis		Current evaluation	
	NICE TA429[16]	NICE TA689[4]	Chosen values	Justification
Modelling approach	PSM; cost-utility	PSM; cost-minimisation	PSM; cost-minimisation	This approach has been applied in previous HTA submissions for BTKi treatments in CLL (TA429, TA689)[4,16] This approach is flexible, and is able to adequately quantify the primary objectives of treating patients with R/R CLL
Approval population	Adults with CLL who have received at least 1 therapy	Previously treated patients with R/R CLL	Adults with R/R CLL who have had at least one previous therapy	Aligned with the licenced indication for zanubrutinib (please refer to Section B.1.1 Decision problem for additional rationale)
Intervention	Ibrutinib	Acalabrutinib	Zanubrutinib	In line with the final NICE scope
Comparators	Palliative care composed of: Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (10%) BR (35%) FCR (10%) Rituximab with high-dose methylprednisolone (25%) Chlorambucil (20%) Secondary comparators of BR, immuno-oncology and ofatumumab	Ibrutinib	Acalabrutinib and ibrutinib	In line with the final scope (please refer to Section B.1.1 Decision problem, description of the technology and clinical care pathway for additional rationale)
Perspective	UK NHS and PPS	UK NHS and PPS	UK NHS and PPS	Consistent with NICE reference case[101]
Time horizon	20 years	30 years	Lifetime (30 years)	Lifetime horizon (30 years) is required to capture all differences in treatment arms in the economic model
Cycle length	4-week	4-week	4-week	Consistent with design of ALPINE which uses a period of 4 weeks for drug administration cycles

Factor	Previous evaluations for BTKis		Current evaluation	
	NICE TA429[16]	NICE TA689[4]	Chosen values	Justification
Half-cycle correction	Yes	Yes	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and end of each cycle
Source for clinical efficacy	RESONATE; Study OMB114242; CLL2M GCLLSG; HELIOS; Study 119; Study 116	RESONATE, ASCEND	ALPINE, ASCEND, ELEVATE-RR	PFS and OS were derived from the ALPINE trial for zanubrutinib ASCEND and ELEVATE-RR trials are used in the MAICs versus acalabrutinib
Safety	RESONATE	RESONATE, ASCEND	ALPINE; ASCEND	Safety data from key clinical trials for treatment arms
Utilities	RESONATE; Beusterien 2010[102]	N/A	Base-case: N/A Scenario: NICE TA561[126] and Holzner 2004[104]	A cost-minimisation approach was used. A cost-utility analysis was provided as a scenario, utilising data from NICE TA561[126] and Holzner 2004[104]
Costs	Treatment acquisition and administration Disease management End-of-life Management of Grade 3 or above adverse events Subsequent therapies	Treatment acquisition and administration Disease management End-of-life Management of Grade 3 or above adverse events Subsequent therapies	Treatment acquisition and administration Disease management End-of-life Management of Grade 3 or above adverse events Subsequent therapies	Consistent with NICE reference case[101]
Outcomes	Total (aggregated and disaggregated) costs, LYs and QALYs Incremental costs, LYs and QALYs ICER	Total (aggregated and disaggregated) costs and LYs Incremental costs and LYs	Base-case: Total (aggregated and disaggregated) costs and incremental costs Scenario: LYs, QALYs, incremental LYs and QALYs and ICER	Consistent with the final scope for this appraisal and the NICE reference case[101]
Uncertainty	OWSA Scenario analysis Probabilistic sensitivity analysis	OWSA Scenario analysis Probabilistic sensitivity analysis	OWSA Scenario analysis Probabilistic sensitivity analysis	Consistent with the NICE reference case[101]

*Incremental QALYs and ICERs were presented within the cost-utility scenario analyses only

BR – Bendamustine + rituximab; BTKi – Burton tyrosine kinase inhibitor; CLL – Chronic lymphocytic leukaemia; FCR – Fludarabine-cyclophosphamide-rituximab; HTA – Health technology assessment; ICER – Incremental cost-effectiveness ratio; LY – Life year; MAIC – Matching-adjusted indirect comparison; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; N/A – Not applicable; OS – Overall survival; OWSA – One-way sensitivity analysis; PFS – Progression-free survival; PSM – Partitioned survival model; PPS – Personal Social Services; QALY – Quality-adjusted life year; R/R – Relapsed or refractory; UK – United Kingdom.

B.3b.2.1 Patient population

The CMA evaluates the cost-difference of treatment with zanubrutinib compared with both acalabrutinib and ibrutinib in patients with R/R CLL who have had at least one previous therapy. The baseline characteristics for the modelled population are presented in Table 100.

Table 100: Baseline characteristics for modelled population

Characteristics	Mean (SE)	Source
Age (years)	[redacted]	ALPINE CSR Table 14.1.2.1
Weight (kg)	[redacted]	ALPINE CSR Table 14.1.2.1
BSA (m^2)	1.92 (0.21)	Calculation
Proportion female	[redacted]	ALPINE CSR Table 14.1.2.1

CSR – Clinical study report; kg – Kilogram; m – Metre; N/A – Not applicable; SE – Standard error.

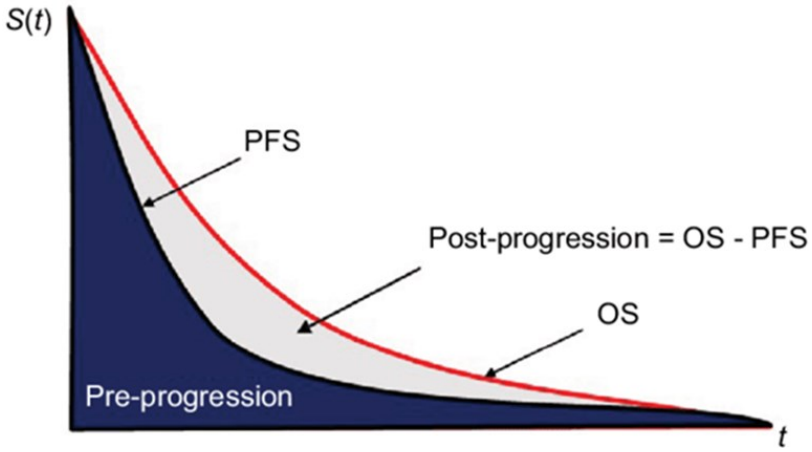
B.3b.2.2 Model structure

The CMA was performed within a full cost-effectiveness model framework. As illustrated in Figure 57, a 3-health state PSM was developed. The model utilises three mutually exclusive health states to model patients' survival outcomes over the time horizon: PF, PD, and death. All patients initiate in the PF health state and can transition to the PD health state upon disease progression. In a PSM, state occupancy is estimated by extrapolating trial data for the cumulative probability of PFS and OS for the duration of the time horizon.

A four-week (28 day) cycle length was used to accommodate the administration schedule of treatment regimens, whilst allowing sufficient granularity to accurately capture differences in cost and health effects between cycles. A lifetime (30 year) time horizon allowed long-term treatment costs to be captured.

Total costs of treatments were estimated by combining the proportion of patients in each health state over time with the costs assigned to the respective state.

Figure 57: Health state structure used in the economic model



PD – Progressed disease; PF – Progression-free.

B.3b.2.3 Health states

The model structure includes the following health states:

- **PF**: All patients initiate in the PF state and receive treatment until either discontinuation, progression or death. After the first cycle of treatment, patients can discontinue treatment whilst remaining in the PF state until either progression or death.

- **PD**: The PD state captures patients who have progressed and moved on to a subsequent line of treatment, with patients occupying this health state until death. After the first cycle of subsequent treatment, patients can discontinue treatment whilst remaining in the PD state until death.

- **Death**: The death state is an absorbing state, meaning that patients cannot transition out of the health state upon entering.

B.3b.2.4 Transitions

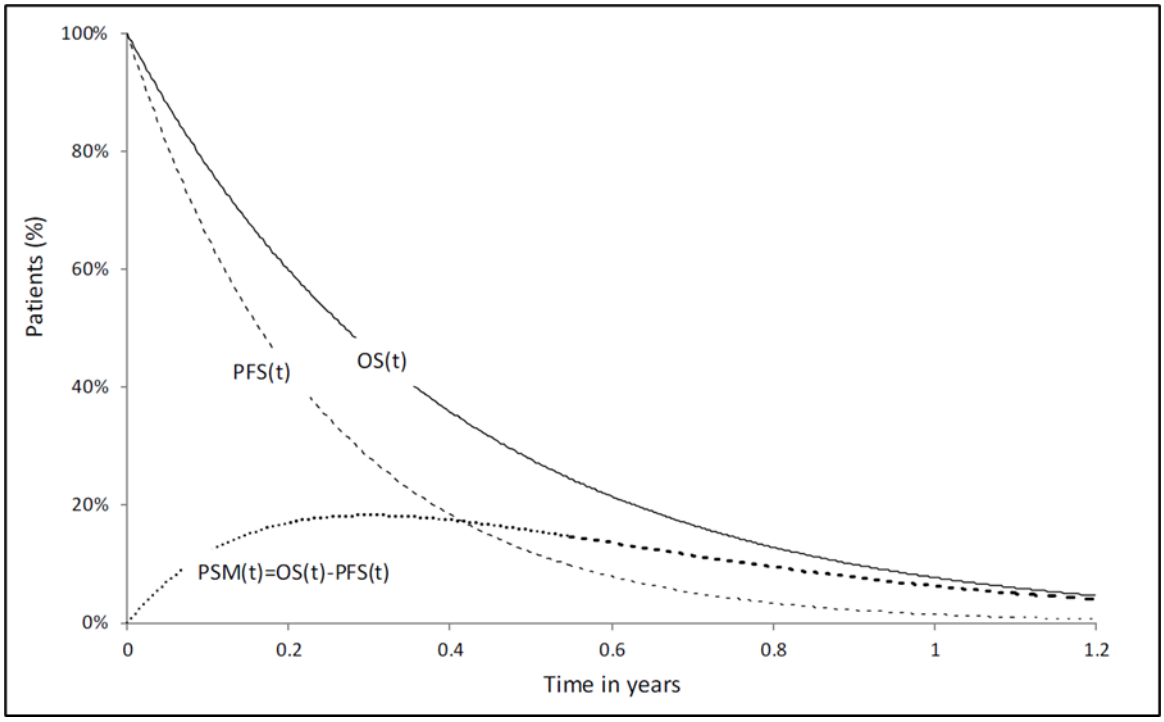
At each model cycle, the number of patients in each independent and mutually exclusive health state is updated with an illustration provided in Figure 58:

- **The proportion of patients who are PF** is represented directly from the PFS(t) curves for each treatment and constrained by OS(t) such that the number of patients who are progression-free cannot exceed the total number of patients alive.

- **The proportion of patients with PD** is calculated by the PSM(t) curve as the difference between OS(t) and PFS(t) to denote all patients alive who are not progression-free.

- **Death** is calculated as 1-OS(t); that is, all patients who are not alive. In the model, OS(t) is constrained by age- and gender-matched UK general population mortality to ensure the disease-related risk of death does not exceed general population.

Figure 58: Illustration of how the PFS and OS curves are used to estimate health state occupancy in the PSM



OS - Overall survival; PFS - Progression-free survival; PSM - Partitioned survival model
Source: NICE DSU 2017[127]

Time on primary treatment is modelled independently from PFS, allowing patients to discontinue treatment despite remaining in the PF state. However, time on first-line treatment is constrained by PFS, reflecting that BTKi treatment should be administered until disease progression or unacceptable toxicity. Following treatment progression, patients can switch to a subsequent active treatment, modelled as a basket of treatments defined by a weighted distribution. Time on subsequent treatment is modelled independently from PD state occupation, allowing patients to complete or discontinue treatment despite remaining in the PD state. Treatment-related costs, such as drug acquisition and drug administration costs, are accrued based on the time on treatment.

B.3b.2.5 Model conceptualisation and justification of approach

The strengths of the partitioned survival approach are well-documented in NICE Decision Support Unit Technical Support Document 19, providing flexibility and directly using trial-based time-to-event endpoints available from the clinical trials.[127] The PSM structure is a widely accepted approach that has been used in previous NICE HTAs in R/R CLL, particularly as it is not necessary to model multiple lines of subsequent therapy given the limited treatment options for patients in the R/R setting.

A PSM approach was selected over a semi-Markov approach as explicit modelling of survival on subsequent treatments was not required and data from ALPINE was sufficiently mature to provide robust extrapolations for PFS and OS. Furthermore, a discrete event simulation was rejected as these models are highly data intensive. Clinical and economic experts in attendance at an advisory board (03 November 2022) held by the Company deemed the PSM structure suitable for the decision problem.[11]

B.3b.2.6 Intervention technology and comparators

The intervention in the model is zanubrutinib. As highlighted in Section B.1.1.1 Comparators, acalabrutinib and ibrutinib are considered the key relevant comparators to zanubrutinib in patients with R/R CLL. This is supported by the 2022 BSH guidelines for the treatment of CLL, by UK clinical expert opinion for 1:1 interviews, quantitative prescribing data from IQVIA and an advisory board (03 November 2022) conducted by the Company.[7–9,11,105] Details of the dosing used in the model can be found in Table 101.

Table 101: Dosing regiments in the economic model

Drug	Dosing regimen	Source
Zanubrutinib	320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or unacceptable toxicity	Zanubrutinib SmPC[2]
Ibrutinib	420 mg administered orally once daily until PD or unacceptable toxicity	Ibrutinib SmPC[106]
Acalabrutinib	100 mg administered orally twice daily until PD or unacceptable toxicity	Acalabrutinib SmPC[2]

PD – Progressed disease; mg – Milligram; SmPC – Summary of Product Characteristics.

B.3b.3 Clinical parameters and variables

Individual survival analyses were required to estimate movement between health states. The key clinical parameters and variables in the model which required separate survival analyses were: PFS, OS and TTD (for cost calculations only).

B.3b.3.1 Time-to-event analysis

Parametric survival analysis was conducted by fitting survival functions to patient-level survival data collected in ALPINE to estimate long-term extrapolations. The ALPINE 2021 DCO was used to inform the economic model. The survival analyses to inform the economic model, along with the MAICs were performed in Q1-3 2022, prior to the publication of late breaking data from the ALPINE 2022 DCO in December 2022. There was insufficient time to update the cost-effectiveness analyses and the MAICs ahead of the submission deadline. The results from the 2022 DCO confirm the findings of the 2021 DCO, and as such are not expected to impact the conclusions of the economic analyses and indicate that the assumption of non-inferiority of zanubrutinib versus ibrutinib in the model is conservative.

The survival analysis was conducted in line with the methods recommended by NICE DSU 14, using the following distributions: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma.[85] The process of selecting a best-fitting distribution is described in Figure 2 in Section B.3a.3.1. and involved an assessment of clinical plausibility leveraging clinical expert opinion and comparing to real-world data, coupled with an assessment of statistical fit via measures such as AIC and BIC. The extrapolated curves were also visually compared against the KM data from ALPINE to assess fit over the observed data period. The most clinically plausible and best-fitting models were selected for the model base case with the impact of selecting alternative curves considered in sensitivity analysis.

B.3b.3.2 PFS

To align with the MAIC analyses performed (see Section B.2.9 Indirect and mixed treatment comparisons) and primary endpoint from ALPINE, extrapolations based on the INV-assessed PFS endpoint are presented in the base case, with extrapolations using IRC-assessed PFS endpoint presented as a scenario analysis. Details of IRC-assessed PFS KM curves and parametric model statistics are provided in Appendix M.

PFS was directly derived from IPD from the ALPINE trial. As of the data cut-off of December 2021, [redacted] ([redacted]%) progression events were observed in the zanubrutinib arm. In order to test the uncertainty in the extrapolations, scenario analyses were conducted using the December 2020 data cut for PFS and OS with the associated KM curves and parametric model statistics provided in Appendix M.

The goodness-of-fit statistics for the INV-assessed PFS endpoint for zanubrutinib are presented in Table 102. Based on the AIC and BIC statistics, the log-logistic distribution provided the best statistical fit (AIC) to the observed data for zanubrutinib, and the Weibull

distribution provided the second-best statistical fit (AIC). However, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.[108]

Table 102: Goodness-of-fit statistics for INV-assessed PFS – zanubrutinib (ALPINE)

Distribution	Zanubrutinib (Stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; INV – Investigator; PFS – Progression-free survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for INV-assessed PFS for zanubrutinib are presented in Figure 59. The Gompertz model provides the most conservative estimations, followed by the Weibull model. The remaining parametric functions exhibit tails which plateau.

Figure 59: KM for INV-assessed PFS overlaid with extrapolated parametric survival curves – zanubrutinib (ALPINE)

INV - Investigator; KM – Kaplan-Meier; PFS – Progression-free survival.

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for PFS and additional clinical validation of the curve selection was required. Feedback received from an advisory board conducted by the Company (03 November 2022) suggested that ~50% of patients would be expected to be progression-free at 50 months (4.16 years), in line with the expected PFS for acalabrutinib in the ASCEND trial (62% PF at 42 months) and in excess of the 44.1 month median PFS observed in RESONATE given the

statistically significant improvement in PFS observed for zanubrutinib in ALPINE.[11,93,128] Landmark PFS rates for zanubrutinib are presented in Table 103.

Table 103: Landmark INV-assessed PFS – zanubrutinib (ALPINE)

Distribution	Median (months)	PFS (%) at landmark timepoints*					
		1-year	5-year	10-year	15-year	20-year	30-year
Weibull							
Log-normal							
Log-logistic							
Exponential							
Generalised Gamma							
Gompertz							

*Using generalised gamma OS to ensure PFS was not capped by OS.
INV – Investigator; OS – Overall survival; PFS – Progression-free survival.

The Weibull distribution produced extrapolations at which 50% of patients were progression-free at 4.52 years in line with the rates stated by clinical experts and was selected to inform the PFS extrapolations in the base case.[11] Sensitivity analyses were conducted using the Gompertz curve which provided the next closest estimation of median PFS at 3.89 years.

B.3b.3.3 OS

OS was directly projected based on the KM data reported in the ALPINE trial. As of the data cut-off of December 2021, [redacted] ([redacted]%) death events were observed in the zanubrutinib arm. In order to test the uncertainty in the extrapolations, scenario analyses were conducted using the December 2020 data cut for PFS and OS with the associated KM curves and parametric model statistics provided in Appendix M.

The goodness-of-fit statistics for the OS endpoint for zanubrutinib are presented in Table 104. Based on the AIC and BIC statistics, the exponential distribution provided the best statistical fit (AIC) to the observed data for zanubrutinib, and the log-normal distribution provided the second-best statistical fit (AIC). However, all distributions are considered a reasonable statistical fit as they are within zero-four AIC points of the best fitting curve.[108]

Table 104: Goodness-of-fit statistics for OS – zanubrutinib (ALPINE)

Distribution	Zanubrutinib (Stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; OS – Overall survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for OS for zanubrutinib are presented in Figure 60. The Weibull model provides the most conservative estimations, followed by the exponential model. The remaining parametric functions exhibit tails which plateau.

Figure 60: KM for OS overlaid with extrapolated parametric survival curves – zanubrutinib (ALPINE)

KM – Kaplan-Meier; OS – Overall survival.

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for OS and additional clinical validation of the curve selection was required. Feedback received from an advisory board conducted by the Company (03 November 2022) suggested that ~50% of patients would be expected to be alive at 10 years.[11] Landmark OS rates for zanubrutinib are presented in Table 105.

Table 105: Landmark OS – zanubrutinib (ALPINE)

Distribution	Median (months)	OS (%) at landmark timepoints					
		1-year	5-year	10-year	15-year	20-year	30-year
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal							
Log-logistic							
Exponential							
Generalised Gamma							

Distribution	Median (months)	OS (%) at landmark timepoints					
		1-year	5-year	10-year	15-year	20-year	30-year
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS – Overall survival.

The Weibull model was selected to inform OS extrapolations in the base case because it produced the extrapolation at which ~50% of patients were alive at 10 years (median OS at 10.54 years) in line with the rates stated by clinical experts.[11]

Sensitivity analyses were conducted using the exponential curve which provided the next closest estimation of median OS at 12.15 years.

B.3b.3.4 Treatment duration

The model base case assumes that all BTKis are given until progression in line with the respective SmPCs. This assumption was validated by UK clinical experts in attendance at an advisory board (03 November 2022) organised by the Company.[11]

An alternative approach of modelling extrapolated TTD data from ALPINE for both zanubrutinib and ibrutinib was explored and presented as a scenario analysis. No TTD data were available in the literature for acalabrutinib, so no alternative approaches were explored for this treatment.

Details of the TTD KM curves and parametric model statistics are provided in Appendix M.

B.3b.3.5 Relative efficacy

B.3b.3.5.1 Comparison with acalabrutinib in RR CLL patients

As discussed in Section B.2.9 Indirect and mixed treatment comparisons , two MAICs were conducted both of which demonstrated that zanubrutinib is at least non-inferior to acalabrutinib in patients with R/R CLL – one conducted using ELEVATE-RR and one using ASCEND, as shown in Table 106.

Table 106: Summary of MAIC results for zanubrutinib vs acalabrutinib for patients with R/R CLL – ELEVATE-RR

	PFS (IRC) hazard ratio (95% CI)	OS hazard ratio (95% CI)
MAIC using ELEVATE-RR		
Model 1	[redacted]	[redacted]
Model 2	[redacted]	[redacted]
MAIC using ASCEND		
Model 1	[redacted]	[redacted]

	PFS (IRC) hazard ratio (95% CI)	OS hazard ratio (95% CI)
Model 2	[redacted]	[redacted]

CI – Confidence interval; CLL – Chronic lymphocytic leukaemia; MAIC – Matching-adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or recurrent.

The MAICs presented make the best use of the available evidence for zanubrutinib and acalabrutinib**.** Feedback received from an advisory board conducted by the Company (03 November 2022) agreed that the HRs were **clinically plausible** for PFS and noted that the similarity between the unadjusted and adjusted PFS and OS KMs for zanubrutinib and acalabrutinib supported the non-inferiority of zanubrutinib to acalabrutinib.[11]

Therefore, as discussed in Section B.3b.2 Economic analysis, a CMA was conducted versus acalabrutinib which assumed equivalence of zanubrutinib to acalabrutinib across all time-to-event endpoints.

B.3b.3.5.2 Comparison with ibrutinib in R/R CLL patients

The ALPINE trial met its primary endpoint, with zanubrutinib demonstrating a statistically significant improvement in ORR determined by INV-assessment. Clinical superiority of zanubrutinib over ibrutinib was supported by consistently better outcomes in secondary endpoints. At the 2021 data cut-off, when compared to treatment with ibrutinib, treatment with zanubrutinib was associated with a statistically significant 45% reduction in the risk of INV-assessed disease progression or death (HR: 0.55; 95% CI: 0.39 to 0.76); p=0.0004). The PFS benefit of zanubrutinib was confirmed in late breaking data, which after a median follow-up of approximately 30 months demonstrated that zanubrutinib was associated with a statistically significant 31% reduction in both INV-assessed and IRC-assessed progression or death compared to ibrutinib (HR: 0.69; 95% CI 0.49 – 0.86).[77] Furthermore, median PFS was not reached in the zanubrutinib group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group, highlighting the significant improvement in PFS in patients treated with zanubrutinib compared to ibrutinib.[77]

Given that the ALPINE trial showed clinical superiority of zanubrutinib over ibrutinib, using a CMA to model the cost-effectiveness of zanubrutinib versus ibrutinib in patients with R/R CLL is a conservative approach. However, to remain consistent with the approach used to model the cost-effectiveness of zanubrutinib in patients with untreated CLL, a CMA was conducted versus ibrutinib. The CMA assumed equivalence of zanubrutinib to ibrutinib across all time-to-event endpoints, as discussed in Section B.3b.2 Economic analysis.

B.3b.3.5.3 Assessment of uncertainty

To model non-inferiority within the model, the following steps were taken:

- A HR of 1 (versus zanubrutinib) was assumed for both acalabrutinib and ibrutinib for PFS and OS.

- Time on treatment was assumed to be equal across zanubrutinib, acalabrutinib and ibrutinib with all BTKis modelled to be given until progression.

- Patients received the same subsequent treatments following progression, with 80% of patients receiving venetoclax-rituximab and 20% of patients receiving idelalisib-rituximab.

The sensitivity of the results to the CMA approach, assuming equal efficacy of zanubrutinib compared to acalabrutinib and ibrutinib, respectively, were explored within probabilistic and deterministic sensitivity analyses, as per the NICE methods guides.[112] Furthermore, cost-utility analyses are also explored in which the OS and PFS HR generated in the MAICs are applied to acalabrutinib and direct extrapolations from the ALPINE trial are used for ibrutinib.

B.3b.3.6 Summary of base-case inputs

The data sources and chosen distributions or parameters to inform the base case are presented in Table 107.

Table 107: Data sources and distributions used to inform base-case clinical parameters

Clinical parameter	Data source	Chosen distribution/input
PFS	ALPINE for zanubrutinib, HR=1 applied for acalabrutinib and ibrutinib	Weibull
OS	ALPINE for zanubrutinib, HR=1 applied for acalabrutinib and ibrutinib	Weibull
TTD	ALPINE for all BTKis	Until treatment progression

BTKi – Bruton tyrosine kinase inhibitor; HR – Hazard ratio; OS – Overall survival; PFS – Progression-free survival; TTD – Time to treatment discontinuation.

B.3b.4 Measurement and valuation of health effects used for scenario analyses

Patients with R/R CLL typically experience worse HRQoL compared to the general population across several domains, including symptom burden, mental functioning, and physical functioning – see Section B.1.3.2 Burden of CLL for further information.

B.3b.4.1 Health-related quality-of-life data from clinical trials

The ALPINE trial collected HRQoL data using EQ-5D-5L at baseline and every 12 weeks from the start of Cycle 1 until disease progression, and then every 24 weeks in the long-term follow-up after disease progression.

B.3b.4.2 Mapping

In line with the NICE reference case, the EQ-5D-5L indices were then mapped to EQ-5D-3L indices using the crosswalk algorithm published by Hernandez-Alava (2022) to generate utility scores.[112,113] Once mapped, the EQ-5D-3L utility scores at all visits were analysed using a mixed-effects linear regression with a random intercept for each patient to account for repeated measures. The potential effect of treatment and progression status on utility was explored both individually, and jointly in the same model. All regression models were adjusted for baseline utility (centred at the mean value of the eligible population) to consider between-patient differences in utilities at baseline.

As there was no evidence of systematic differences in QoL across study arms, the utility values generated by pooling across treatments were deemed most appropriate to inform the model to increase the sample size of the analysis. The mean EQ-5D utility scores from ALPINE are presented by treatment and visit in Figure 61.

Figure 61: Trial generated EQ-5D per treatment and visit – ALPINE

CI – Confidence interval; EQ-5D – EuroQoL Five Dimensions.

The predicted utility for each health state from the model compared to utilities based on published general population in the UK is presented in Table 77. Progression was assessed by INV to align with the PFS endpoint used in the base-case survival analysis. The mean PF and PD utility scores were higher than the estimates for age-matched, condition-stratified UK general population. As such, the utility values from ALPINE trial lack face validity with results

potentially impacted by immaturity of data. This issue also occurred in NICE TA689, in which trial utility values were higher than the age- and gender-matched UK population.[78]

Table 108: Utility Model Including Progression Status as Predictors

Predictor	No. of Patients	No. of Obs.	Coefficient (95% CI)	Source
Predicted utility for health states				
PF	[redacted]	[redacted]	[redacted]	ALPINE
PD	[redacted]	[redacted]	[redacted]	
Mean utility based on published general population in UK				
General population irrespective of health status (65 to ⩽70)			0.804 (0.790, 0.817)	Ara and Brazier 2011[45]; supplementary Table A4
General population with health condition "cancer" (65 to ⩽70)			0.730 (0.652, 0.807)	
General population without health condition "cancer" (65 to ⩽70)			0.808 (0.794, 0.821)	

CI – Confidence interval; PD – Progressed disease; PF – Progression-free

B.3b.4.3 Health-related quality-of-life studies

Results of the SLR conducted to identify studies reporting on the HRQoL of patients with CLL is reported Section B.3a.4.3 Health-related quality of life studies . Full details of the process and methods used to identify and select the HRQoL data relevant to the technology being evaluated are presented in Appendix H.

The SLR identified ten HRQoL studies which were deemed relevant to this appraisal. A summary of these studies is provided in Section B.3a.4.3 Health-related quality of life studies .

B.3a.4.4 Age-related disutility

The base case included an age-related adjustment to account for the deterioration in HRQoL with age. The age-related adjustment was implemented using the methods descried in Ara and Brazier 2011 and applied each cycle for the duration of the time horizon.[103] The utility decrements were estimated for all patients alive in each model cycle using the following equation:

$$HS_{utility} * (1 - (0.9508566 + 0.0212126 * (\%\, male) - 0.0002587 * age - 0.0000332 * age^2))$$

B.3b.4.5 Adverse reactions

The model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥2% of study subjects receiving treatment (across any BTKi treatment option). Events occurring in

≥2% of patients were considered appropriate to capture AEs that would impact patients in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. The Grade ≥3 AEs included in the model are reported in Table 79.

Within the base case, AEs in the model only have an impact on costs with AE-related costs applied to the proportion of patients experiencing the event in the first cycle of the model. A sensitivity analyses is explored which assessed the impact of AEs on HRQoL, with utility decrements applied to the proportion of patients experiencing the event in the first cycle of the model.

It is assumed that all AEs occur and are resolved in the first four weeks of treatment. In addition, only AEs associated with primary treatment were considered, and AEs associated with subsequent lines were not considered.

Table 109: Grade ≥3 treatment-related AEs occurring in ≥2% of patients by treatment

Treatment	Zanubrutinib	Ibrutinib	Acalabrutinib
Anaemia	2.47%	2.47%	11.69%
Thrombocytopenia	2.78%	3.09%	3.90%
Pneumonia	4.01%	7.41%	5.19%
Neutropenia	14.20%	13.89%	15.58%
Hypertension	13.27%	12.96%	1.95%
Neutrophil count decreased	4.32%	4.01%	1.30%
Source	ALPINE CSR Table 14.3.1.2.3.5[76]		ASCEND Ghia 2020[86]

AE – Adverse event; CSR – Clinical study report.

In the sensitivity analysis assessing the impact of AEs on HRQoL, the model estimated the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates, the mean utility decrements associated with these AEs, and the mean duration of each AE episode. Utility decrements associated with AEs were sourced from previous NICE appraisals in CLL and published literature as the impact of AEs on HRQoL was not explicitly collected in the ALPINE study. The duration of AEs was derived from the same data sources wherever available. All AE utility decrements were applied in Cycle 1.

The utility decrements and duration estimates for AE used in the analysis are presented in Table 80.

Table 110: Utility decrements and duration estimates by AE

AE	Disutility	Source	Duration (days)	Source
Anaemia	–0.090	TA487[59]	23.21	TA487[59]
Thrombocytopenia	–0.110	TA487[59]	23.21	TA487[59]
Pneumonia	–0.195	Tolley 2013[61]	18.20	TA359[58]
Neutropenia	–0.163	TA487[59]	15.09	TA487[59]
Hypertension	–0.020	Wehler 2018[62]	21.00	Assumption
Neutrophil count decreased	–0.163	TA487[59]	15.09	TA487[59]

AE – Adverse event; TA – Technology appraisal.

B.3b.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

As a CMA is being presented as the base-case analysis, the HRQoL impact is equalised across treatments and the impact on HRQoL is only considered in sensitivity analysis using a cost-utility approach.

As the utility values from ALPINE trial lacked face validity, published utility values identified within the SLR were used to inform the cost-utility scenario. In NICE TA561, a PF utility of 0.748 and PD utility of 0.6 were accepted. The PF utility of 0.748 was informed by utilities reported in TA561, generated using EQ-5D estimates based on relapsed CLL patients on rituximab treatment in Study 116.[19] The PD utility of 0.60 was informed by Holzner et al. (2004).[104] In Holzner et a. (2004), QoL was measured using the EORTC QLQ-C30 and the

FACIT: General questionnaire in 418 cancer patients, 81 of whom had CLL. The utility value of 0.60 has been accepted in a number of previous NICE appraisals in CLL. The utilities used in the cost-utility scenario analysis are presented in Table 81.

Table 111: Summary of utility values for the cost-utility scenario analysis

State	Utility value: mean (standard error)	95% CI	Source
PF	0.748 (0.0740)	0.589, 0.879	Utilities reported in TA516, generated using EQ-5D estimates from Study 116[19]
PD	0.600 (0.0597)	0.481, 0.714	Holzer et al. 2004[104]

CI – Confidence interval; EQ-5D – EuroQoL Five Dimensions; PD – Progressed disease; PF – Progression-free; TA – Technology appraisal.

B.3b.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify studies reporting on the cost and resource use of patients with R/R CLL. Full details of the process and methods used to identify and select the cost and resource use data relevant to the technology being evaluated are presented in in Appendices I.

The SLR identified three cost and resource use studies from a UK perspective and two NICE appraisals for patients with R/R CLL.

Consistent with the studies identified in the SLR, the following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of primary and subsequent treatment
- Medical resource use costs
- The cost of unplanned events, such as AEs and terminal care costs.

For cost inputs, a NHS and PSS perspective was adopted. Unit costs of drug acquisition, administration, resources use, and AE management were based on standard costing sources. The types and frequencies of resources associated with disease management, monitoring, and terminal care were derived based on previous NICE appraisals or consulted with clinical experts.

B.3b.5.1 Intervention and comparators' costs and resource use

B.3b.5.1.1 Drug acquisition costs

Drug acquisition costs were based on the dosing regimens presented in Table 112 and costs per pack and cycle are presented in Table 83. Dosing information was sourced from the respective SmPCs and costs were sourced from the BNF. In instances where multiple pack prices were available, the pack price with the lowest cost per mg was used. [redacted]

As discussed in Section B.3b.3.4 Treatment duration, primary treatment with BTKi is given until disease progression in the base case and scenario analyses were explored with alternative treatment duration assumptions.

Following disease progression, it is assumed that the majority of patients receive treatment with BCL2i (venetoclax-rituximab), with a small proportion receiving treatment with idelalsib-rituximab. This is aligned with 2022 BSH guidelines, which recommend a 'sequencing' approach, whereby the optimal treatment following progression of patients treated with front-line treatment with a BTKi, a BCL2i is recommended.[5] Therefore, the model assumes that following disease progression, 80% of patients receive venetoclax-rituximab and 20% of patients receive idelalsib-rituximab. This assumption was validated by clinical, health economic and statistical experts at an advisory board (03 November 2022) held by the Company.[11]

Table 112: Dosing regimen of treatments included in the economic model

Treatment	Dosing regimen	Source
Zanubrutinib	320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or unacceptable toxicity	Zanubrutinib SmPC[2]
Acalabrutinib	100 mg administered orally twice daily until PD or unacceptable toxicity.	Acalabrutinib SmPC[107]
Ibrutinib	420 mg administered orally once daily until PD or unacceptable toxicity.	Ibrutinib SmPC[106]
Idelalisib-rituximab *(Subsequent treatment only)*	Idelalisib: 150 mg administered orally twice daily until PD or unacceptable toxicity. Rituximab: first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 IV on day one of each cycle for a maximum of six cycles.	Idelalisib SmPC[123]
Venetoclax-rituximab *(Subsequent treatment only)*	Venetoclax: 20 mg once daily for 7 days, gradually increasing to 400mg over a period of 5 weeks. 400 mg administered orally once daily for a total of two years. Rituximab: first dose at 375 mg/m^2, subsequent doses at	Venetoclax SmPC[111]

Treatment	Dosing regimen	Source
	500 mg/m^2 IV on day one of each cycle for a maximum of six cycles.	

PD – Progressed disease; IV – Intravenous; SmPC – Summary of Product Characteristics.

The model considers wastage for IV drugs in the base case, for treatments that depend on BSA, namely rituximab, as there is a potential that some of the drug will be wasted if perfect vial sharing is not practiced. A BSA of 1.92m^2 (SD: 0.20 m^2) was calculated from ALPINE. Relative dosing intensity is assumed at 100% for all treatments. Relative dosing intensity is assumed at 100% for all treatments, aligned with the assumption accepted in NICE TA689.[4]

Table 113: Drug package price and cost per cycle

Treatment	Dosage strength	Pack size/vial volume	Administration route	Cost per pack (£)	Cost per cycle (£)
Zanubrutinib	80 mg	120	Oral	[redacted]	[redacted]
Acalabrutinib	100mg	60	Oral	5,059.00	4,721.73
Ibrutinib	420 mg	28	Oral	4,292.40	4,292.40

mg – Milligram. Source British National Formulary 2022[122]

Table 114: Subsequent treatments drug package price and total acquisition cost

Treatment	Dosage strength	Pack size/vial volume	Admin route	Cost per pack (£)	Mean duration of treatment (cycles)	Total acquisition cost (£)
Idelalisib	150mg	60	Oral	3,311.80	20.3	71,359.86
Rituximab	10mg/ml 10mg/ml	10ml 50ml	IV	157.17 785.84	8	
Venetoclax	100mg	7	Oral	299.34	26	130,008.37
Rituximab	10mg/ml 10mg/ml	10ml 50ml	IV	157.17 785.84	6	

Source: Idelalisib SmPC;[129] Seymour et al. (2018);[130] Sharman et al. (2019);[131] Venetoclax SmPC.[111] IV – Intravenous.

B.3b.5.1.2 Drug administration costs

Drug administration costs were applied to CIT drugs with costs varying between initial and subsequent administrations. Targeted non-CIT therapies that are orally administered did not incur administration costs. Unit costs for all categories of administration were based on National Schedule of NHS Costs and are presented in Table 84.

Table 115: Drug administration costs

Description of cost	Use in model	Unit cost (£)	Source
Delivered oral chemotherapy	Idelalisib: one administration within Cycle 1	54.00	National Schedule of NHS Costs 2020/21[123]
Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance	Rituximab: one administration within Cycle 1	526.52	National Schedule of NHS Costs 2020/21[123]
Deliver Subsequent Elements of a Chemotherapy Cycle	Rituximab: one administration per cycle for Cycles 2-6 or Cycles 2-8	470.62	National Schedule of NHS Costs 2020/21[123]

NHS – National Health Service.

B.3b.5.2 Health-state unit costs and resource use

Costs related to routine follow-up and disease management included in the model are as reported in Section B.3a.5.2 Health-state unit costs and resource use.

B.3b.5.3 Adverse reaction unit costs and resource use

As described in Section B.3b.4.5 Adverse reactions, the model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ⩾2% of study subjects receiving treatment (across any BTKi treatment option). Total AE costs were calculated as the product of the AE incidence, as presented in Table 79, and the respective unit cost as presented in Table 86. It is assumed that all AEs occur and are resolved in the first four weeks of treatment and only AEs associated with first-line treatment were considered.

Table 116: AE management costs

Adverse event	Cost (£)	Source	Comment
Anaemia	721.99	National Schedule of NHS Costs 2020/21[123]	SA09 Other Red Blood Cell Disorders with CC Score 0-5, non-elective short stay
Hypertension	537.86	National Schedule of NHS Costs 2020/21[123]	EB04Z Hypertension, non-elective short stay
Neutropenia	761.01	National Schedule of NHS Costs 2020/21[123]	SA35 Agranulocytosis, non-elective short stay
Neutrophil count decreased	761.01	National Schedule of NHS Costs 2020/21[123]	SA35 Agranulocytosis, non-elective short stay
Pneumonia	782.27	National Schedule of NHS Costs 2020/21[123]	DZ11 Lobar, Atypical or Viral Pneumonia, non-elective short stay
Thrombocytopenia	881.88	National Schedule of NHS Costs 2020/21[123]	SA12 Thrombocytopenia, non-elective short stay

AE – Adverse event; CC – Complication and comorbidity; NHS – National Health Service.

B.3b.5.4 Miscellaneous unit costs and resource use

B.3b.5.4.1 Terminal care costs

Costs for terminal care included in the model are as reported in Section B.3a.5.4.1 Terminal care costs.

B.3b.5.4.2 TLS management costs

Costs for TLS management included in the model are as reported in Section B.3a.5.4.2 TLS management costs.

B.3b.6 Severity

As a CMA is presented, the severity weight calculations were not considered relevant to this appraisal.

B.3b.7 Uncertainty

The key uncertainties in the economic evaluation relate to the immaturity of data. The long-term extrapolations are informed by less than half of the trial population and so are associated with uncertainty. Furthermore, the immaturity of data led to wide confidence intervals in the MAICs. However, the uncertainty in the MAIC results were alleviated in the cost-minimisation approach. In addition, the long-term extrapolations, assumptions on survival and estimates of comparative efficacy were validated with clinical, health economic and statistical experts at an advisory board (03 November 2022) held by the Company.[11]

Furthermore, the uncertainty in the model results were explored through extensive DSA, PSA, and scenario analyses. In the DSA, each variable was systematically increased and decreased based on 95% confidence intervals or published ranges. In the absence of data, the higher and lower values were calculated as ± 20% of the mean base-case value.

In the PSA, values were drawn at random for each variable from its uncertainty distribution. The model allowed the beta, gamma, log-normal, normal, and Dirichlet distributions to be used and also included Cholesky decomposition matrix calculation fields for modelling pairs of input parameters for which the covariance structure between two variables was known, such as for the survival curves (Table 88).

A number of scenario analyses were also performed to assess the impact of alternative assumptions and data sources which were not captured within the DSA and PSA.

Table 117: Distribution options by model parameter for PSA

Parameter	Distribution
Proportion of female	Beta distribution
Starting age, BSA (m^2), weight	Normal distribution
PFS, OS, TTD survival extrapolations	Normal distribution (Cholesky decomposition)
HRs of PFS, OS	Log-normal distribution
Risk of experiencing AEs	Beta distribution
Subsequent treatment duration	Gamma distribution
Health state related utility	Beta distribution
Utility decrement due to AEs	Normal distribution
Duration of AE	Gamma distribution
Disease management and monitoring costs AE management costs Subsequent treatment costs TLS prophylaxis treatment costs	Gamma distribution
Proportion of patients by TLS related risk	Dirichlet distribution
Proportion of patients receiving subsequent treatment	Dirichlet distribution

AE – Adverse event; BSA – Body surface area; HR – Hazard ratio; OS – Overall survival; PFS – Progression-free survival; TLS – Tumour lysis syndrome; TTD – Time to discontinuation.

B.3b.8 Managed access proposal

A managed access proposal is not considered relevant for zanubrutinib for treating patients with R/R CLL.

B.3b.9 Summary of base-case analysis inputs and assumptions

B.3b.9.1 Summary of base-case analysis inputs

A summary of the key parameters used in the CMA is presented in Table 118.

Table 118: Summary of variables applied in the economic model

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model settings			
Population	ALPINE	N/A	B.3a.2 Economic analysis
Perspective	Payer (UK NHS and PPS)	N/A	
Time horizon	Lifetime (30 years)	Not modelled	
Proportion females	[redacted]	95% CI (0.282, 0.353) (Beta)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Starting age in model (years)	[redacted]	SE: 0.38 (Normal)	
Weight (kg)	[redacted]	SE: 0.67 (Normal)	
Body surface area (m^2)	1.92	SE: 0.01 (Normal)	
Half-cycle correction	Yes	Fixed	
Discount rate (cost and outcomes)	3.5%	Fixed	
Clinical parameters			
Efficacy			
PFS – distribution	Weibull	DSA: Normal PSA: Cholesky	B.3a.3 Clinical parameters and variables
OS – distribution	Weibull		
Treatment duration for BTKis	Treat until disease progression		
Hazard ratio			
Zanubrutinib versus acalabrutinib	1.00	Fixed in CMA	B.3a.3 Clinical parameters and variables
Zanubrutinib versus ibrutinib	1.00	Fixed in CMA	
Probability of AE – zanubrutinib			
Anaemia	0.0247	Sample size (324) used to model variance around the mean (Beta)	B.3a.4 Measurement and valuation of health effects
Hypertension	0.1327		
Neutropenia	0.1420		
Neutrophil count decreased	0.0432		
Pneumonia	0.0401		
Thrombocytopenia	0.0278		
Probability of AE – ibrutinib			
Anaemia	0.0247	Sample size (324) used to model variance around the mean (Beta)	B.3a.4 Measurement and valuation of health effects
Hypertension	0.1296		
Neutropenia	0.1389		
Neutrophil count decreased	0.0401		
Pneumonia	0.0741		
Thrombocytopenia	0.0309		
Probability of AE – acalabrutinib			
Anaemia	0.1169	Sample size (154) used to model variance around the mean (Beta)	B.3a.4 Measurement and valuation of health effects
Hypertension	0.0195		
Neutropenia	0.1558		
Neutrophil count decreased	0.0130		
Pneumonia	0.0519		

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Thrombocytopenia	0.0390		
Duration of adverse event (days)			
Anaemia	23.21	SE: 4.64 (Gamma)	B.3a.4 Measurement and valuation of health effects
Hypertension	21.00	SE: 4.20 (Gamma)	
Neutropenia	15.09	SE: 3.02 (Gamma)	
Neutrophil count decreased	15.09	SE: 3.02 (Gamma)	
Pneumonia	18.20	SE: 3.64 (Gamma)	
Thrombocytopenia	23.21	SE: 4.64 (Gamma)	
Health-related quality-of-life parameters (scenario only)			
Health state utilities			
PF	0.7480	SE: 0.0740 (Beta)	B.3a.4 Measurement and valuation of health effects
PD	0.6000	SE: 0.0597 (Beta)	
Disutilities			
Anaemia	-0.0900	SE: 0.0180 (Beta)	B.3a.4 Measurement and valuation of health effects
Hypertension	-0.0200	SE: 0.0040 (Beta)	
Neutropenia	-0.1630	SE: 0.0326 (Beta)	
Neutrophil count decreased	-0.1630	SE: 0.0326 (Beta)	
Pneumonia	-0.1950	SE: 0.0390 (Beta)	
Thrombocytopenia	-0.1100	SE: 0.0220 (Beta)	
Cost parameters			
Disease management resource use			
PF: Full blood count	0.31	SE: 0.06 (Gamma)	B.3a.5 Cost and healthcare resource use identification
PF: LDH	0.23	SE: 0.05 (Gamma)	
PF: Haematologist visits	0.15	SE: 0.03 (Gamma)	
PD: Full blood count	0.61	SE: 0.12 (Gamma)	
PD: LDH	0.00	SE: 0.00 (Gamma)	
PD: Haematologist visits	0.46	SE: 0.09 (Gamma)	
PD: CT scan	0.15	SE: 0.03 (Gamma)	
PD: Bone marrow exam	0.08	SE: 0.02 (Gamma)	
PD: Inpatient visit (non-surgical)	0.31	SE: 0.06 (Gamma)	
Disease management costs			
Full blood count	£3.63	SE: £0.73 (Gamma)	B.3a.5 Cost and healthcare
LDH	£1.85	SE: £0.37 (Gamma)	
Haematologist visits	£157.89	SE: £31.58 (Gamma)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
CT scan	£105.66	SE: £21.13 (Gamma)	resource use identification
Bone marrow exam	£574.44	SE: £114.89 (Gamma)	
Inpatient visit (non-surgical)	£750.17	SE: £150.03 (Gamma)	
End-of-life costs			
Terminal care	£7,000.72	SE: £1,400.14 (Gamma)	B.3a.5 Cost and healthcare resource use identification
TLS management resource use			
Proportion of patients: Low	17.53%	SE: 3.51% (Dirichlet)	B.3a.5 Cost and healthcare resource use identification
Proportion of patients: Intermediate	54.64%	SE: 10.93% (Dirichlet)	
Proportion of patients: High	27.84%	SE: 5.57% (Dirichlet)	
TLS management costs			
Low	£1,430.40	SE: £286.08 (Gamma)	B.3a.5 Cost and healthcare resource use identification
Intermediate	£2,016.54	SE: £403.31 (Gamma)	
High	£2,146.81	SE: £429.36 (Gamma)	
Adverse event costs			
Anaemia	£721.99	SE: £144.40 (Gamma)	B.3a.5 Cost and healthcare resource use identification
Hypertension	£537.86	SE: £107.57 (Gamma)	
Neutropenia	£761.01	SE: £152.20 (Gamma)	
Neutrophil count decreased	£761.01	SE: £152.20 (Gamma)	
Pneumonia	£782.27	SE: £156.45 (Gamma)	
Thrombocytopenia	£881.88	SE: £176.38 (Gamma)	
Treatment acquisition costs			
Zanubrutinib cost per pack	[redacted]	Fixed	B.3a.5 Cost and healthcare resource use identification
Ibrutinib cost per pack	£4,292.40	Fixed	
Acalabrutinib cost per pack	£5,059.00	Fixed	
Treatment acquisition costs – subsequent treatment			
Venetoclax-rituximab one-off cost	£71,359.86	Fixed	B.3a.5 Cost and healthcare resource use identification
Idelalisib-rituximab one-off cost	£130,008.37	Fixed	
Treatment administration costs			

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Delivered oral chemotherapy	£54.00	SE: £5.51 (Gamma)	B.3a.5 Cost and healthcare resource use identification
Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£526.52	SE: £53.72 (Gamma)	
Subsequent Elements of a Chemotherapy Cycle	£470.62	SE: £48.02 (Gamma)	
Distribution of subsequent treatment			
Venetoclax-rituximab	80%	Fixed	B.3a.5 Cost and healthcare resource use identification
Idelalisib-Rituximab	20%	Fixed	

AE – Adverse Event; BTK – Bruton tyrosine kinase; CT – Computerised tomography; LDH – Lactate dehydrogenase; N/A – Not applicable; NHS – National Health Service; OS – Overall survival; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival; SE – Standard error; TLS – Tumour Lysis Syndrome; UK – United Kingdom.

B.3b.9.2 Assumptions

The key assumptions made in the model base case are presented in Table 119.

Table 119: Key assumptions in the model

Model input	Assumption	Rationale
Time horizon	Lifetime	In line with NICE guidance[112] (assumed a 30-year life time horizon based on the age of the patient population in the ALPINE trial).
Equal efficacy between zanubrutinib and alternative BTKis	A cost-minimisation analysis is used, assuming non-inferiority between zanubrutinib, acalabrutinib and ibrutinib. PFS and OS curves are therefore assumed equivalent across all BTKis.	As discussed in Section B.3b.3.5 Relative efficacy, zanubrutinib is non-inferior to both acalabrutinib and ibrutinib in patients with R/R CLL. Due to the wide confidence intervals produced in the MAIC, a cost-minimisations approach was considered appropriate. This assumption was validated with clinical experts.
Treatment duration	All patients treated with BTKis are assumed to be treated until progression	As per the respective SmPCs, patients are treated until progression meaning that treatment duration is informed by PFS in the model.
Treatment administration costs	No administration costs for BTKis	Regimens administered orally can be taken by patients at home. It is assumed that no costs are incurred.

Model input	Assumption	Rationale
Subsequent treatment costs	80% of patients are assumed to receive VR and 20% are assumed to receive IR as a subsequent treatment upon progression	To reflect UK clinical practice following feedback received at an advisory board (03 November 2022) held by the Company.[11]
Disease management and monitoring	Disease management and monitoring costs are assumed equal across treatment arms	It is assumed that monitoring of patients and associated costs will not vary across treatment arms.

BTK – Bruton tyrosine kinase; CLL – Chronic lymphocytic leukaemia; IR - Idelalisib-Rituximab; MAIC – Matching-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; PFS – Progression-free; R/R – Relapsed or refractory; SmPC – Summary of product characteristic; VR – Venetoclax-rituximab.

B.3b.10 Base-case results

B.3b.10.1 Base-case cost-minimisation analysis results

The base-case results are presented in Table 120. Over a lifetime time horizon, treatment with zanubrutinib in patients with R/R CLL was associated with cost-savings of [redacted] and [redacted] per person, compared to ibrutinib and acalabrutinib, respectively.

Disaggregated results from the base-case analysis are presented in Appendix J.

Table 120: Base-case deterministic results in patients with R/R CLL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

LYG – Life years gained; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

B.3b.11 Exploring uncertainty

B.3b.11.1 Probabilistic sensitivity analysis

PSA was conducted in order to assess the impact of parameter uncertainty on the results of the analysis in the model base case; 1,000 simulations were performed, and for each simulation, a value was drawn at random for each variable from its uncertainty distribution simultaneously, and the resulting costs, outcomes, and incremental results were recorded.

The results of the base-case PSA are presented in Table 121 and the total cost and QALY scatterplot is presented in Figure 62. Based on the PSA, treatment with zanubrutinib in patients with R/R CLL was associated with cost-savings of [redacted] and [redacted], for ibrutinib

and acalabrutinib, respectively. The mean probabilistic results lie close to the deterministic results, indicating that the model is robust to parameter uncertainty.

Table 121: Base-case PSA results in patients with R/R CLL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

LYG – Life years gained; PSA – Probabilistic sensitivity analysis; QALY – Quality-adjusted life year; R/R – Relapsed or refractory.

Figure 62: Total cost and QALY scatterplot for zanubrutinib vs ibrutinib and acalabrutinib in patients with R/R CLL

CLL – Chronic lymphocytic leukaemia; QALY – Quality-adjusted life year; R/R – Relapsed or refractory.

B.3b.11.2 Deterministic sensitivity analysis

DSA was performed to explore the effect of uncertainty associated with varying individual model inputs or groups of individual model inputs. The results of the DSA are summarised in Table 122 and Figure 63 for ibrutinib and Table 123 and Figure 64 for acalabrutinib. The most influential factors on the DSA were the parameters used in the Weibull models to project PFS for zanubrutinib and the cost of subsequent treatments.

Table 122: DSA results (incremental costs) for zanubrutinib vs ibrutinib in patients with R/R CLL

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Weibull model to project PFS for Zanubrutinib	[redacted]	[redacted]
Cost of subsequent treatments modelled as one-off cost following therapy with Zanubrutinib	[redacted]	[redacted]

Parameter name	Lower incremental costs	Upper incremental costs
Cost of subsequent treatments modelled as one-off cost following therapy with Ibrutinib	[redacted]	[redacted]
Scale for Weibull model to project PFS for Zanubrutinib	[redacted]	[redacted]
Cost of AEs per cycle with Ibrutinib	[redacted]	[redacted]
Cost of AEs per cycle with Zanubrutinib	[redacted]	[redacted]
Intercept for Weibull model to project OS for Zanubrutinib	[redacted]	[redacted]
Scale for Weibull model to project OS for Zanubrutinib	[redacted]	[redacted]
Disease management cost per cycle Progression-free state	[redacted]	[redacted]

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or refractory.

Table 123: DSA results (incremental costs) for zanubrutinib vs acalabrutinib in patients with R/R CLL

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Weibull model to project PFS for Zanubrutinib	[redacted]	[redacted]
Cost of subsequent treatments modelled as one-off cost following therapy with Zanubrutinib	[redacted]	[redacted]
Cost of subsequent treatments modelled as one-off cost following therapy with Acalabrutinib	[redacted]	[redacted]
Scale for Weibull model to project PFS for Zanubrutinib	[redacted]	[redacted]
Cost of AEs per cycle with Acalabrutinib	[redacted]	[redacted]
Cost of AEs per cycle with Zanubrutinib	[redacted]	[redacted]
Intercept for Weibull model to project OS for Zanubrutinib	[redacted]	[redacted]
Scale for Weibull model to project OS for Zanubrutinib	[redacted]	[redacted]
Disease management cost per cycle Progression-free state	[redacted]	[redacted]

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis OS – Overall survival; PFS – Progression-free survival.

Figure 63: Tornado plot of DSA results (incremental costs) for zanubrutinib vs ibrutinib in patients with R/R CLL

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or refractory.

Figure 64: Tornado plot of DSA results (incremental costs) for zanubrutinib vs acalabrutinib in patients with R/R CLL

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or refractory.

B.3b.11.3 Scenario analysis

Details of each of the included scenario analyses are presented in Table 95. Deterministic and probabilistic scenario analysis results for zanubrutinib versus both ibrutinib and acalabrutinib are presented in Table 96 and Table 126 below, respectively. The probabilistic results lie are consistent with the deterministic results, indicating the robustness of the analyses to parameter uncertainty.

Zanubrutinib was more effective and less costly than acalabrutinib in the cost-utility scenario analyses using HRs generated from Model 1 and Model 2 of the MAIC with ELEVATE-RR. In addition, zanubrutinib was slightly less effective than acalabrutinib in the cost-utility scenario analyses using the HRs generated from Model 1 and Model 2 of the MAIC with ASCEND. However, due to large cost-savings of patients treated with zanubrutinib compared to acalabrutinib, zanubrutinib remained cost-effective in these scenarios (ICER versus acalabrutinib > £30,000 in the south-west quadrant of the incremental cost-effectiveness plane). Overall, when considering the mean incremental costs and QALYs over the four cost-utility scenarios versus acalabrutinib, zanubrutinib was more effective and less costly and hence dominates acalabrutinib. The cost-utility analyses demonstrate the uncertainty in the MAIC results and support the use of the CMA approach in the base case.

Zanubrutinib was more effective and less costly than ibrutinib in the cost-utility scenario analysis using data extrapolated from the ALPINE trial and hence dominates ibrutinib. This supports the fact that using a CMA in the base case is a conservative approach.

Table 124: Summary of scenario analyses

Base-case	Scenario analysis	Scenario analysis description
3.5% discount rate	No discounting	0% discount is assumed for costs to assess the impact of discounting
3.5% discount rate	High discount rates (6%)	6% discount is assumed for costs to assess the impact of discounting
December 2021 data cut for PFS and OS	December 2020 data cut for PFS and OS	December 2020 data cut for ALPINE PFS and OS is used to assess the impact on survival estimates

Base-case	Scenario analysis	Scenario analysis description
PFS endpoint (INV)	PFS endpoint (IRC)	IRC PFS is used to assess the impact on survival estimates
PFS curve for zanubrutinib (Weibull)	PFS curve for zanubrutinib (Gompertz)	Gompertz distribution modelled for ALPINE PFS
OS curve for zanubrutinib (Weibull)	OS curve for zanubrutinib (Exponential)	Exponential normal distribution modelled for ALPINE OS
Include wastage	Exclude wastage	Wastage for IV treatments is excluded in the analysis
Include AE costs	Exclude AE costs	The impact of AEs on total costs is excluded from the analyses
Use PFS data for zanubrutinib and ibrutinib	Use TTD data for zanubrutinib and ibrutinib	ALPINE TTD data extrapolated and model for zanubrutinib and ibrutinib time on treatment
Exclude AE impact to QALYs	Apply AE impact to QALYs	The impact of AEs on QALYs is included in the analysis
CMA (ALPINE data)	Cost-utility (Ibrutinib ALPINE extrapolation)	A cost-utility analysis utilising extrapolated trial data from ALPINE versus ibrutinib
	Cost-utility (acalabrutinib MAIC 1 ELEVATE-RR)	A cost-utility analysis utilising the ELEVATE-RR MAIC Model 1 versus acalabrutinib
	Cost-utility (acalabrutinib MAIC 1 ASCEND)	A cost-utility analysis utilising the ASCEND MAIC Model 1 versus acalabrutinib
	Cost-utility (acalabrutinib MAIC 2 ELEVATE-RR)	A cost-utility analysis utilising the ELEVATE-RR MAIC Model 2 versus acalabrutinib
	Cost-utility (acalabrutinib MAIC 2 ASCEND)	A cost-utility analysis utilising the ASCEND MAIC Model 2 versus acalabrutinib

AE – Adverse event; BTKi – Bruton tyrosine kinase inhibitor; IRC – Independent review committee; IV – Intravenous; survival; MAIC – Match adjusted indirect comparison; TTD – Time to treatment discontinuation; R/R – Relapsed/refractory; QALY – Quality-adjusted life year.

Table 125: Summary of scenario analyses results for zanubrutinib vs ibrutinib and acalabrutinib – deterministic

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base Case	[redacted]	-	-	-	[redacted]	-	-	-
No Discounting	[redacted]	-	-	-	[redacted]	-	-	-
High Discount rates (6%)	[redacted]	-	-	-	[redacted]	-	-	-
December 2020 data cut for PFS and OS	[redacted]	-	-	-	[redacted]	-	-	-
PFS endpoint (IRC)	[redacted]	-	-	-	[redacted]	-	-	-
PFS curve for zanubrutinib (Gompertz)	[redacted]	-	-	-	[redacted]	-	-	-
OS curve for zanubrutinib (Exponential)	[redacted]	-	-	-	[redacted]	-	-	-
Exclude wastage	[redacted]	-	-	-	[redacted]	-	-	-
Exclude AE costs	[redacted]	-	-	-	[redacted]	-	-	-
Use TTD data for zanubrutinib and ibrutinib	[redacted]	-	-	-	[redacted]	-	-	-
Apply AE impact to QALYs	[redacted]	0.0000	0.0003	Dominant	[redacted]	0.0000	0.0005	Dominant
Cost-utility (Ibrutinib ALPINE extrapolation)	[redacted]	1.0252	0.8010	Dominant	[redacted]	-	-	-
Cost-utility (acalabrutinib MAIC 1 ELEVATE-RR)	-	-	-	-	[redacted]	1.7225	1.1365	Dominant
Cost-utility (acalabrutinib MAIC 1 ASCEND)	-	-	-	-	[redacted]	-0.2961	-0.0564	Less costly less effective
Cost-utility (acalabrutinib MAIC 2 ELEVATE-RR)	-	-	-	-	[redacted]	1.6545	1.0989	Dominant

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cost-utility (acalabrutinib MAIC 2 ASCEND)	-	-	-	-	[redacted]	-1.2369	-0.6428	Less costly less effective
Cost-utility (acalabrutinib mean increment costs and mean incremental QALYs using ASCEND/ELEVATE-RR)	-	-	-	-	[redacted]	0.4610	0.3840	Dominant

AE – Adverse event; BTKi – Bruton tyrosine kinase inhibitor; ICER – Incremental cost-effectiveness ratio; IRC – Independent review committee; LYG – Life year gained; MAIC – Matching-adjusted indirect comparison; PFS – Progression-free survival; TTD – Time to treatment discontinuation; R/R – Relapsed/refractory; QALY – Quality-adjusted life year

Table 126: Summary of scenario analyses results for zanubrutinib vs ibrutinib and acalabrutinib – probabilistic (n=1,000 iterations)

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base Case	[redacted]	-	-	-	[redacted]	-	-	-
No Discounting	[redacted]	-	-	-	[redacted]	-	-	-
High Discount rates (6%)	[redacted]	-	-	-	[redacted]	-	-	-
December 2020 data cut for PFS and OS	[redacted]	-	-	-	[redacted]	-	-	-
PFS endpoint (IRC)	[redacted]	-	-	-	[redacted]	-	-	-
PFS curve for zanubrutinib (Gompertz)	[redacted]	-	-	-	[redacted]	-	-	-
OS curve for zanubrutinib (Exponential)	[redacted]	-	-	-	[redacted]	-	-	-

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Exclude wastage	[redacted]	-	-	-	[redacted]	-	-	-
Exclude AE costs	[redacted]	-	-	-	[redacted]	-	-	-
Use TTD data for zanubrutinib and ibrutinib	[redacted]	-	-	-	[redacted]	-	-	-
Apply AE impact to QALYs	[redacted]	0.000	0.000	Dominant	[redacted]	0.000	0.000	Dominant
Cost-utility (Ibrutinib ALPINE extrapolation)	[redacted]	0.988	0.778	Dominant	[redacted]	-	-	-
Cost-utility (acalabrutinib MAIC 1 ELEVATE-RR)	-	-	-	-	[redacted]	1.156	0.791	Dominant
Cost-utility (acalabrutinib MAIC 1 ASCEND)	-	-	-	-	[redacted]	-0.363	-0.117	Less costly less effective
Cost-utility (acalabrutinib MAIC 2 ELEVATE-RR)	-	-	-	-	[redacted]	1.109	0.787	Dominant
Cost-utility (acalabrutinib MAIC 2 ASCEND)	-	-	-	-	[redacted]	-1.235	-0.679	Less costly less effective
Cost-utility (acalabrutinib mean increment costs and mean incremental QALYs using ASCEND/ELEVATE-RR)	-	-	-	-	[redacted]	0.1669	0.1955	Dominant

AE – Adverse event; BTKi – Bruton tyrosine kinase inhibitor; ICER – Incremental cost-effectiveness ratio; IRC – Independent review committee; LYG – Life year gained; MAIC – Matching-adjusted indirect comparison; PFS – Progression-free survival; TTD – Time to treatment discontinuation; R/R – Relapsed/refractory; QALY – Quality-adjusted life year.

B.3b.12 Subgroup analysis

As per the final scope, no subgroup analyses were conducted as subgroups were not considered relevant to this appraisal to evaluate the cost-difference of treatment with zanubrutinib compared with both acalabrutinib and ibrutinib in patients with R/R CLL who have had at least one previous therapy.

B.3b.13 Benefits not captured in the QALY calculation

Please refer to Section B.3a.13 Benefits not captured in the QALY calculation for details of benefits not captured in the QALY calculation when comparing treatment with zanubrutinib to both acalabrutinib and ibrutinib in patients with R/R CLL who have had at least one previous therapy.

B.3b.14 Validation

Upon completion of the model programming, a rigorous and comprehensive quality check of the model was conducted, following the same steps outlined in Section B.3a.14 Validation.

The modelled survival outputs were also validated against long-term published data in patients with R/R CLL from the ASCEND and RESONATE trials. Given the superiority of zanubrutinib compared to ibrutinib in the ALPINE trial as discussed in Section B.3b.3.5.2 Comparison with ibrutinib in R/R CLL patients, it is clinically plausible that the projected PFS and OS extrapolations of zanubrutinib align better with the second-generation BTKI acalabrutinib in the ASCEND trial. As can be seen in Table 127, the outputs for PFS and OS for the three BTKis under the non-inferiority assumption closely align to the clinical trial data, increasing the validity of the results.

Table 127: Comparison of modelled PFS and OS versus published clinical trial data in R/R CLL

Dataset	Proportion of patients at 1 year	Proportion of patients at 3 years	Proportion of patients at 6 years
PFS			
Modelled BTKis	[redacted]	[redacted]	[redacted]
RESONATE ibrutinib arm[93]	84%	59%	31%
ASCEND acalabrutinib arm[86]	90%	65%	NR
OS*			
Modelled BTKis	[redacted]	[redacted]	[redacted]

Dataset	Proportion of patients at 1 year	Proportion of patients at 3 years	Proportion of patients at 6 years
RESONATE ibrutinib arm[93]	90%	73%	48%
ASCEND acalabrutinib arm[86]	95%	81%	NR

BTKi – Bruton tyrosine kinase inhibitor; CLL – Chronic lymphocytic leukaemia; NR – Not reached; OS – Overall survival; PFS – Progression-free survival.

B.3b.15 Interpretation and conclusions of economic evidence

B.3b.15.1 Summary

A 3-health state PSM was developed to evaluate the cost saving of zanubrutinib versus relevant comparators in patients with R/R CLL:

- Acalabrutinib in patients with R/R CLL, aligned with the recommendations made by NICE in TA689.[4]
- Ibrutinib in patients with R/R CLL, aligned with the recommendations made by NICE in TA429.[16]

The model structure was chosen to model patients' survival outcomes in the 3-health states (PF and PD, and death) with the structure providing flexibility and directly using trial-based time-to-event endpoints available from the clinical trials. The PSM structure is a widely accepted approach that has been used in previous NICE HTAs in R/R CLL, particularly as it is not necessary to model multiple lines of subsequent therapy given the limited treatment options for patients in the R/R setting. For the base case, a non-inferiority assumption of equalised efficacy was assumed across all three BTKis, based on results from multiple MAICs and clinical expert opinion. Sensitivity analyses in the form of cost-utility analyses were conducted to relax this non-inferiority assumption.

Clinical data were primarily sourced from the pivotal trial for zanubrutinib in patients with R/R CLL, ALPINE. Safety data were sourced from ALPINE and the key comparator clinical trial (ASCEND). The model included treatment cost categories relevant to a UK NHS and PPS perspective, with costs and resource input sourced from appropriate UK based sources. Utilities were considered in sensitivity analysis using a cost-utility approach, with utility data sourced from published literature and aligned with NICE/EAG preferred assumptions in NICE TA561 and TA689. [4,126]

Overall, the results of the economic analysis are considered generalisable to UK clinical practice.

B.3b.15.2 Summary of cost-minimisation estimates

In the base-case analysis, the CMA demonstrated a cost saving of [redacted] versus ibrutinib and [redacted] for zanubrutinib versus acalabrutinib in patients with R/R CLL. In addition, as discussed in Section B.3b.3.5.2 Comparison with ibrutinib in R/R CLL patients, using a CMA to model the cost-effectiveness of zanubrutinib versus ibrutinib is a conservative approach, further supporting the fact that zanubrutinib is a cost-effective use of resource for the NHS.

Results from the OWSA indicated that analysis was most sensitive to survival coefficients for the Weibull PFS curve.

Probabilistic results over 1,000 iterations were consistent with the deterministic results for the base case and all scenarios conducted, indicating that the model was robust to parameter uncertainty. Across all scenario analyses conducted, zanubrutinib remained cost saving compared to acalabrutinib and ibrutinib. Cost-utility analyses conducted to explore the impact of relaxing the non-inferiority assumptions indicated that zanubrutinib was less costly than both acalabrutinib and ibrutinib across all scenarios and hence was a cost-effective against both treatment alternatives (both deterministically and probabilistically).

B.3.16 Summary of results

Results of the cost-minimisation analyses showed that zanubrutinib provides the same health benefits as acalabrutinib and ibrutinib at a lower incremental cost both in the first-line and R/R settings. Therefore, zanubrutinib can be considered a cost-effective option for the treatment of:

- previously untreated adults with CLL, without a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable (‘unfit’)
- previously untreated adults with CLL, with a 17p deletion and/or TP53 mutation and in whom CIT is unsuitable (‘high-risk’)
- adults with R/R CLL who have had at least one previous therapy.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Summary of Information for Patients (SIP)

February 2023

File name	Version	Contains confidential information	Date
ID5078_Zanubrutinb for treatment chronic lymphocytic leukaemia_SIP	V1.0	No	3rd February 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic name: Zanubrutinib Brand name: BRUKINSA

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Zanubrutinib is being appraised by NICE for the following patient populations: A. Adult patients with chronic lymphocytic leukaemia who have not previously received treatment and are unable to receive treatment with chemo-immunotherapy (e.g. fludarabine-based therapy and bendamustine-based therapy). B. Adult patients with chronic lymphocytic leukaemia who have not previously received treatment, who have high-risk genetic factors (17p deletion and/or TP53 mutation) and are unable to receive treatment with chemo-immunotherapy. C. Adults with chronic lymphocytic leukaemia who have either relapsed following initial treatment or are refractory to treatment, and who have received had at least one previous therapy. Patients who are suitable for treatment with chemo-immunotherapy and have not previously received treatment for their disease have not been included within the submission for zanubrutinib. This is due to a lack of clinical trial evidence for zanubrutinib in this patient population. However, the Company are willing to explore this population if the available data is deemed relevant by NICE as there is a key unmet need for a new mechanism of action in this population and to avoid equality issues in younger and fitter

patients who could be denied access to a new treatment option that is efficacious, well-tolerated and improves patient choice.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On the 13th October 2022, the European Committee for Medicinal Products for Human Use recommended a change to the terms of the marketing authorisation for zanubrutinib, to include the new indication for the treatment of adult patients with chronic lymphocytic leukaemia (https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-brukinsa-ii-03_en.pdf). BRUKINSA monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia in Europe following approval by the European Medicines Association on the 17th November 2022.[1] On the 6th January 2023, zanubrutinib was also approved in the UK for the treatment of adult patients with chronic lymphocytic leukaemia by the Medicines and Healthcare products Regulatory Agency through the European Commission Decision Reliance Procedure.[2,3]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

None.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Chronic lymphocytic leukaemia is a cancer of the blood and bone marrow and the most common form of leukaemia. It accounts for 1% of total cancer cases in the UK between 2016 and 2018.[4] Chronic lymphocytic leukaemia is rare in people under 40 years of age and mostly affects people over 60 years old.[5] Approximately 3,803 new cases of chronic lymphocytic leukaemia are diagnosed each year in England and Wales, equating to ten

new cases a day, with new cases more likely to develop in men than women. The mortality rate is high with approximately 976 deaths due to chronic lymphocytic leukaemia in the UK each year, equating to nearly three deaths each day.[6]

Chronic lymphocytic leukaemia is a chronic disease associated with a range of debilitating symptoms and impairments to quality of life.[7] Patients diagnosed with early-stage disease often do not experience symptoms and have indolent disease for years before they experience symptoms.[8,9] Once present, symptoms include tiredness, anaemia, fever and weight loss. Symptomatic disease can lead to patients having a higher-than-normal amount of lymphocytes (a type of white blood cell) in their blood, cytopenia - a condition in which there is a lower-than-normal number of blood cells, swelling of the lymph nodes, liver and spleen, recurrent infections, or autoimmune complications.[7,10–12]

The course of chronic lymphocytic leukaemia differs from patient to patient and is dependent on a number of patient and genetic factors. These factors can be used to predict how aggressive the disease will likely be and a patient's prognosis. The key genetic factors that can impact the disease course are mutations to the TP53 gene or deletion of the 17p chromosome. Patients with one or both of these mutations are classed as 'high-risk' and are often not eligible for treatment with chemo-immunotherapy.[20]

As chronic lymphocytic leukaemia is a disease of the elderly, the majority of newly diagnosed patients have at least one comorbidity. These comorbidities can include other malignancies, metabolic disorders, cardiovascular, and respiratory diseases, meaning that more than half of patients with chronic lymphocytic leukaemia may be taking multiple prescription medications per day at the time of diagnosis.[13] Elderly patients with chronic lymphocytic leukaemia also tend to have impaired organ function. As a consequence, patients aged over 65 years or those with comorbidities that limit organ function are often classed as 'unfit' and are not eligible for treatment with chemo-immunotherapy due to the harsh nature of the treatment. Younger patients without comorbidities are often classed as 'fit' and may receive treatment with chemo-immunotherapy.

Patients with chronic lymphocytic leukaemia face a large mental burden, reporting fear of relapse, depression, anxiety and difficulty sleeping.[14,15] Due to the high risk of infection, patients find that they feel isolated because of reduced social interaction.[16] In addition, after the shock of diagnosis, patients can spend a long time with the condition prior to initiating treatment, causing anxiety and uncertainty around their prognosis.[17]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

In the UK, a diagnosis of chronic lymphocytic leukaemia is made based on there being a certain number of B-cells (a type of white blood cell) in the blood stream over the course of three months as defined by the International Workshop on chronic lymphocytic leukaemia (iwCLL).[10,18] Patients who are diagnosed with early-stage disease do not tend to show any symptoms and their disease will grow slowly before the onset of symptoms.[8,9]

Once diagnosed, a patient will have a physical examination and complete blood counts to determine their disease stage. There is a three-stage system used to measure the progression of a patient's disease, called the Binet staging system. This is measured based on the number of red blood cells and platelets and the number of areas of the lymphatic system in the body that are enlarged.[8,9,18,19]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Historically, patients with chronic lymphocytic leukaemia have been treated with chemo-immunotherapy. However, the introduction of targeted cancer drugs, such as Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib and acalabrutinib, and B-cell lymphoma 2 inhibitors such as venetoclax, has significantly reduced the likelihood of cancer growing or spreading in patients with chronic lymphocytic leukaemia, and has reduced the likelihood of cancer-related death.

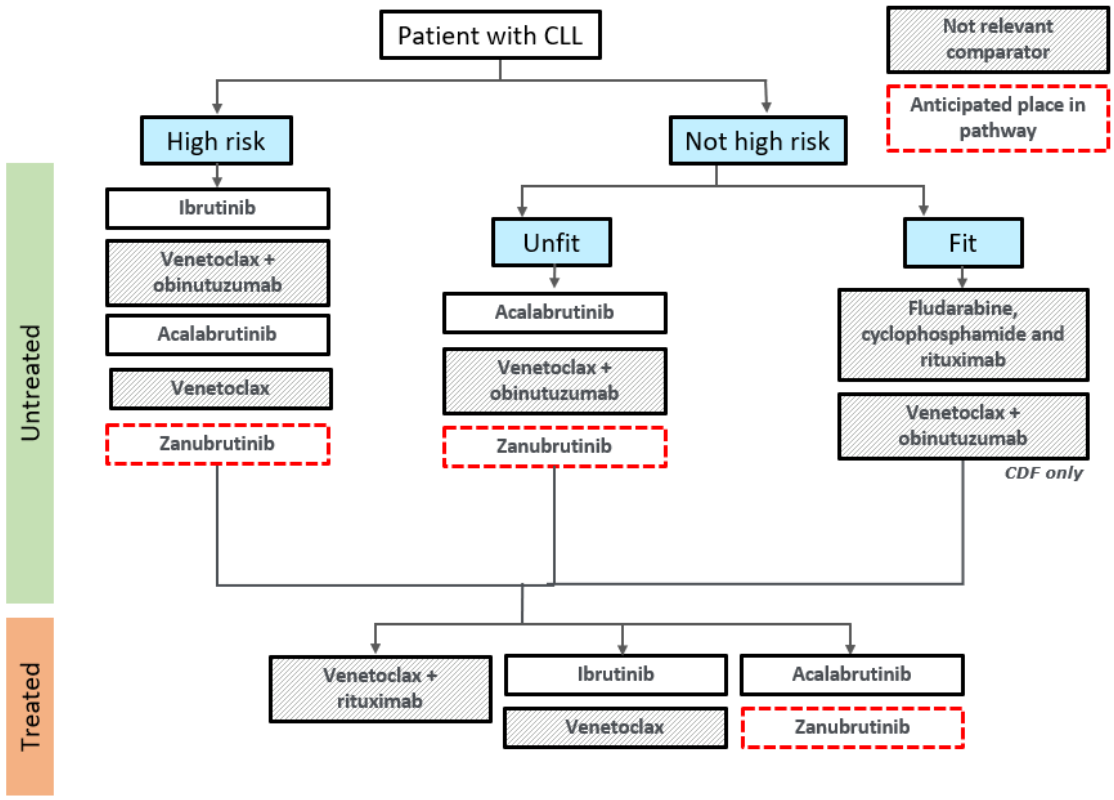
Whilst several different treatment options exist and are approved by NICE for patients with chronic lymphocytic leukaemia, recent clinical guidelines published by the British Society for Haematology in 2022 suggest that the recommended treatment choice in first-line is either a BTK inhibitor, namely acalabrutinib or ibrutinib, or a venetoclax-based regimen with the decision influenced by a number of factors including patient- and clinician-choice.[21]

Clinical experts interviewed during this submission process suggested that venetoclax-based therapy was more often used to treat more 'fit' patients who are younger and do not present with comorbidities and that BTK inhibitors were used more often in 'unfit' and 'high-risk' patients..

Despite the introduction of effective targeted cancer drugs, most patients with chronic lymphocytic leukaemia relapse and need additional therapy. Additionally, a proportion of patients have disease which is refractory to initial treatment.[2] In patients with relapsed/refractory chronic lymphocytic leukaemia who have had at least one previous therapy, choice of treatment is driven by what treatment a patient has previously received with patients progressing following front-line treatment with a BTK inhibitor (i.e. ibrutinib or acalabrutinib), receiving a venetoclax-based regimen and patients progressing following front-line treatment with venetoclax, receiving a BTK inhibitor regimen.

The proposed positioning of zanubrutinib in the treatment pathway, as informed by the 2022 British Society for Haematology guidelines and confirmed by clinicians, is presented in Figure 1.[18] As a next-generation BTK inhibitor, zanubrutinib is not expected to change the decision of whether to treat patients with a BTKi or venetoclax-based therapy and can be considered as an alternative BTK inhibitor treatment.

Figure 1: Clinical pathway of care and proposed positioning of zanubrutinib



CDF – Cancer Drug Fund*; CLL – chronic lymphocytic leukaemia
*The Cancer Drug Fund is a source of funding for cancer drugs in England that was introduced to reduce delays and improve access to promising cancer drugs whilst additional data is being collected.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The course of chronic lymphocytic leukaemia differs from patient to patient and treatment choice is driven by patient factors, such as age, fitness status, presence of comorbidities, and certain cytogenetic factors, such as 17p deletion or TP53 mutation.[10,11] As such, it is important that there are a number of alternative treatment options available as patients can respond differently to treatment. Patient-based evidence about living with chronic lymphocytic leukaemia was gathered during a recent NICE appraisal (NICE TA689[16]) and is summarised below:

- Chronic lymphocytic leukaemia is a complicated disease that is more common in elderly people. After treatment, it is common for the disease to come back and so patients are in a cycle of monitoring, treatment and then relapse. Patients worry that multiple cycles of treatment are likely to impact negatively on their quality of life. Even after successful treatment, patients can experience negative symptoms

and a poor quality of life. Psychologically it is difficult for patients to know that after treatment, it could happen again, and they could require further treatment.[16]

- Chronic lymphocytic leukaemia tends to constantly change, and each time a patient is treated, they respond less well than before. Around 85% of patients who are diagnosed are 65 years or older and might have other medical issues. Therefore, the more toxic treatments will be less well tolerated by elderly patients. To add to this, patients are more vulnerable to catching other illnesses as they are weak from treatment, so they might shield themselves, limiting their ability to socialise and go out and lead normal lives.[16]

- Equality issues arise if BTK inhibitors are only authorised for 'older', less fit patients who are unsuitable for fludarabine-based therapy.[16] In particular, the only non-chemo-immunotherapy treatment option available for younger and fitter patients with chronic lymphocytic leukaemia is venetoclax-obinutuzumab which is available through temporary funding. However, not all patients can tolerate venetoclax-obinutuzumab and patients may prefer a more flexible and less intensive dose regimen. As such, there is a need for more treatment options available for younger, fitter patients with chronic lymphocytic leukaemia.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Zanubrutinib is a next-generation BTK inhibitor. BTK is a protein that plays a key role in the B-cell receptor signalling pathway which helps cancer cells grow and survive. By blocking BTK, zanubrutinib helps kill and reduce the number of cancer cells, which can slow down the worsening of cancer.

Zanubrutinib is highly selective and was designed to address the intolerance and toxicity concerns with first-generation BTK inhibitors (ibrutinib). Ibrutinib is associated with a number of cardiovascular toxicities including atrial fibrillation and flutter, which limit use of this therapy in patients with chronic lymphocytic leukaemia. With fewer off-target effects and a better cardiac safety profile, zanubrutinib has the potential to improve outcomes and reduce side effects compared with first-generation BTK inhibitors.[23]

The Summary of Product Characteristics can be found here: https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf

A patient information leaflet, prepared by BeiGene, can be found here: https://www.brukinsa.com/patient-information.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Currently, zanubrutinib is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended total daily dose of zanubrutinib is 320 mg taken orally either once daily (four x 80 mg capsules) or divided into two doses of 160 mg twice daily (two x 80 mg capsules). Patients must swallow the capsules whole with water (with or without food), and not open, break or chew the capsules. Zanubrutinib should be taken until a patient's disease progresses (as determined by their clinician) or until unacceptable toxicity/side effects are experienced by the patient.

Zanubrutinib is a simple oral regimen and does not require frequent hospital visits. This limits the disruption to both patients' and caregivers' lives who avoid having to travel to the hospital for treatment.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Zanubrutinib has been investigated in CLL in two key head-to-head phase 3 trials, SEQUOIA and ALPINE. A summary of the key clinical trials for zanubrutinib is presented in Table 1.

Table 1: Clinical effectiveness evidence

Study title	**SEQUOIA**[24]	**ALPINE**[25]
Study design	Phase 3, open-label, randomised, multicentre study with multi-cohort design*: • **Cohort 1**: untreated 'unfit' (elderly patients or patients with comorbidities) without a 17p deletion randomised to receive zanubrutinib or bendamustine-rituximab	Phase 3, open-label, randomised, multicentre study

	• **Cohort 2** (single-arm): untreated 'high-risk' patients with a 17p deletion allocated to receive zanubrutinib	

Population	Patients with CLL or SLL in whom FCR treatment is not suitable. Patients must:
	• Have received no prior treatment
	• Be older than 65 years, or between 19-64 years old with one of the following:
	  ○ Creatinine clearance ≥70 mL/min
	  ○ History of previous serious infection or multiple infections in the past 2 years
	  ○ CIRS score >6
		Patients with relapsed or refractory CLL or SLL who are 18 years or older and have received at least one prior treatment

Patient group size	**Cohort 1:** Zanubrutinib (N= 241), bendamustine-rituximab (N= 238) **Cohort 2:** Zanubrutinib (N= 110)	Zanubrutinib (N=327), Ibrutinib (N=325)
Intervention(s)*	Zanubrutinib (Cohort 1, Cohort 2)	Zanubrutinib
Comparator(s)	BR (Cohort 1 only)	Ibrutinib
Key inclusion criteria	• Confirmed diagnosis of CD20-positive CLL or SLL, requiring treatment • Unsuitable for FCR • Measurable disease • ECOG performance status of 0, 1 or 2 • Life expectancy ≥ 6 months. • Adequate bone marrow, renal and hepatic function	• Confirmed diagnosis of CLL or SLL meeting the iwCLL criteria and requiring treatment • Relapsed or refractory to at least one prior systemic therapy for CLL/SLL • Measurable disease • ECOG performance status of 0, 1, or 2 • Life expectancy ≥6 months • Adequate bone marrow, renal and hepatic function
Key exclusion criteria	• Previous systemic treatment for CLL/SLL • Known prolymphocytic leukaemia or history of or suspected Richter's transformation • Clinically significant cardiovascular or pulmonary disease • Prior malignancy • History of severe bleeding, stroke or intracranial haemorrhage	• Known prolymphocytic leukaemia or history of, or currently suspected, Richter's transformation • Clinically significant cardiovascular or pulmonary disease • Prior malignancy • History of severe or spontaneous bleeding, stroke or intracranial haemorrhage • Prior treatment with a BTKi

		• Toxicity from prior anticancer therapy that has not recovered to ≤ Grade 1
Completion date	October 31, 2024 (Estimated)	September 2023 (Estimated)

BR – bendamustine-rituximab; BTKi - Bruton's Tyrosine Kinase inhibitor; CIRS – Cumulative Illness Rating Scale; CLL – Chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; FCR – Fludarabine plus cyclophosphamide and rituximab; iwCLL – International Workshop on Chronic Lymphocytic Leukaemia; SLL – Small lymphocytic lymphoma; *Zanubrutinib-venetoclax is also an intervention within the SEQUOIA trial protocol, however the focus of this appraisal is zanubrutinib monotherapy (aligned with the licensed indication for zanubrutinib in CLL).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Zanubrutinib has been studied in a comprehensive clinical trial programme. The SEQUOIA study provides efficacy and safety data to evaluate zanubrutinib versus bendamustine-rituximab in patients with chronic lymphocytic leukaemia who have not previously received treatment.[24] The ALPINE study provides efficacy and safety data to evaluate zanubrutinib versus ibrutinib in patients with relapsed/refractory chronic lymphocytic leukaemia.[26]

SEQUOIA

The key outcome measured in SEQUOIA was progression-free survival, i.e. the length of time after starting treatment that a patient lives with a disease without it progressing. When comparing treatment with zanubrutinib to bendamustine-rituximab in patients with chronic lymphocytic leukaemia who have not previously received treatment, the SEQUOIA trial found that patients treated with zanubrutinib were 58% less likely to have their disease progress or die than patients treated with bendamustine-rituximab. This improvement was statistically significant, meaning it is not likely due to chance or other factor of interest, and was classed as a meaningful improvement by clinicians. The progression-free survival of patients treated with zanubrutinib was found to be comparable in patients with and without the 17p deletion high-risk genetic factor, meaning that zanubrutinib is consistently effective in patients with CLL regardless of cytogenetic factors. For further information on progression-free survival in SEQUOIA, please see Document B, Sections B.2a.6.1 and B.2a.6.4

Overall survival was also measured in SEQUOIA i.e. the length of time after starting treatment that a patient is alive. As chronic lymphocytic leukaemia is a long-term chronic illness, few death events occurred in SEQUOIA. However, initial results have shown that when compared to treatment with bendamustine-rituximab, treatment with zanubrutinib was associated with a 7% reduction in the risk of death in patients with chronic lymphocytic leukaemia who have not previously received treatment. The overall survival of patients treated with zanubrutinib was found to be comparable in patients with and without the 17p deletion high-risk genetic factor. For further information on overall survival in SEQUOIA, please see Document B, Sections B.2a.6.3 and B.2a.6.4.

Overall response rate measures the proportion of patients who have a response to treatment i.e. the proportion of patients whose tumour disappears or is significantly reduced by a drug. In SEQUOIA, 94.6% of patients treated with zanubrutinib had a tumour that completely disappeared or was partially reduced compared to 85.3% of patients

treated with bendamustine-rituximab. This improvement was statistically significant, meaning it is not likely due to chance or other factor of interest, and was classed as a meaningful improvement by clinicians. The overall response rate of patients treated with zanubrutinib was found to be comparable in patients with and without the 17p deletion high-risk genetic factor. For further information on overall response rate in SEQUOIA, please see Document B, B.2a.6.3 and B.2a.6.4.

ALPINE
The key outcome measured in ALPINE was overall response rate (defined above). In patients with relapsed/refractory chronic lymphocytic leukaemia treated with zanubrutinib, 83.5% had a tumour that completely disappeared or was partially reduced compared to 74.2% of patients treated with ibrutinib. This improvement was statistically significant, meaning it is not likely due to chance or other factor of interest, and was classed as a meaningful improvement by clinicians.[25] For further information on overall response rate in ALPINE, please see Document B, Section B.2b.6.1.

When comparing treatment with zanubrutinib to treatment with ibrutinib in patients with relapsed/refractory chronic lymphocytic leukaemia, the ALPINE trial found that patients treated with zanubrutinib were 45% less likely to have their disease progress or die than patients treated with ibrutinib. This improvement was statistically significant, meaning it is not likely due to chance or other factor of interest, and was classed as a meaningful improvement by clinicians, making zanubrutinib the first BTK inhibitor to show such a difference against an alternative BTK inhibitor. For further information on progression-free survival in ALPINE, please see Document B, Section B.2b.6.3.

Similarly to SEQUOIA, few death events occurred in ALPINE. However, initial results have shown that when comparing to treatment with ibrutinib, zanubrutinib is associated with a 20% reduction in the risk of death in patients with relapsed/refractory chronic lymphocytic leukaemia. For further information on overall survival in ALPINE, please see Document B, Section B.2b.6.3.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patients in SEQUOIA and ALPINE were asked to complete two questionnaires about their quality of life, the EORTC-QLQ-C30 (cancer-specific questionnaire) and the EQ-5D-5L (general health questionnaire). Both questionnaires are commonly used and include questions about multiple topics which contribute to quality of life.

SEQUOIA
In patients with chronic lymphocytic leukaemia who have not previously received treatment, better outcomes were reported by patients treated with zanubrutinib arm reported than patients treated with bendamustine-rituximab when using the EORTC-QLQ-C30 questionnaire. In particular, patients reported improvements in physical functioning, fatigue, nausea/vomiting and diarrhoea. When using the EQ-5D-5L instrument, a similar improvement was seen in general health was seen in patients treated with zanubrutinib and bendamustine-rituximab.[27]

ALPINE
In patients with relapsed/refractory chronic lymphocytic leukaemia, better outcomes were reported by patients treated with zanubrutinib than in patients treated with ibrutinib when using the EORTC-QLQ-C30 questionnaire. In particular, patients reported improvements in physical functioning, fatigue, nausea/vomiting and diarrhoea. When using the EQ-5D-5L instrument, patients treated with zanubrutinib reported a greater improvement in general health than patients treated with ibrutinib. This improvement was statistically significant, meaning it is not likely due to chance or other factor of interest, and was classed as a meaningful improvement by clinicians.[28]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

First-generation BTK inhibitors, such as ibrutinib, are associated with cardiac issues, such as atrial fibrillation or flutter (an irregular and often very rapid heart rhythm that can lead to blood clots in the heart and increase the risk of cardiac issues), which can lead to patients discontinuing treatment and limit the use of BTK inhibitors in patients with pre-existing cardiac issues.[55] As a next-generation BTK inhibitor, zanubrutinib aims to reduce the incidence and severity of cardiac issues experienced by patients.

SEQUOIA
Zanubrutinib is tolerable and safe in the treatment of patients with chronic lymphocytic leukaemia who have not previously received treatment. When compared to patients treated with bendamustine-rituximab, patients treated with zanubrutinib experienced fewer severe adverse events and no new adverse events were identified compared to other BTK inhibitors. Only 3.7% of patients treated with zanubrutinib experienced atrial fibrillation or flutter which was similar to the proportion of patients treated with bendamustine-rituximab experiencing atrial fibrillation or flutter (2.6%). No sudden deaths were reported in either study arm.[27]

ALPINE
Zanubrutinib is tolerable and safe in the treatment of patients with relapsed/refractory chronic lymphocytic leukaemia. When compared to patients treated with ibrutinib, patients treated with zanubrutinib experienced fewer serious adverse events and no new adverse events were identified compared to other BTK inhibitors. Importantly, only 4.6% of patients treated with zanubrutinib experienced atrial fibrillation or flutter which offered a large improvement on the proportion of patients treated with ibrutinib experiencing atrial fibrillation or flutter (12.0%). This improvement was statistically significant, meaning it is not likely due to chance or other factor of interest, and was classed as a meaningful improvement by clinicians.[28]

No deaths were reported due to cardiac issues in patients treated with zanubrutinib compared to five deaths in patients treated with ibrutinib, all of which occurred within 30 days of receiving a dose of ibrutinib. As a next-generation BTK inhibitor, these results support the idea that zanubrutinib reduces the risk of cardiac adverse events that are observed with ibrutinib.[28]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments. • Please include benefits related to the mode of action, effectiveness, safety and mode of administration
- Zanubrutinib is a simple oral regimen and does not require frequent hospital visits. - Zanubrutinib has the potential to reduce the rate of discontinuation due to intolerance or adverse events. - Adverse events associated with zanubrutinib are more tolerable and manageable for patients than those associated with other BTK inhibitors.[29] - Zanubrutinib offers a significant improvement over first-generation BTK inhibitors such as ibrutinib in preventing disease progression and reducing tumour size.[28] - Zanubrutinib offers additional treatment option for physicians to make the best choice for their patients. - Zanubrutinib can be used in patients intolerant to other BTK inhibitors.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments
BTK inhibitors are associated with a number of class-specific side effects including bleeding, hypertension, atrial fibrillation, arthralgias, skin rash, and diarrhoea. The risk of cardiac adverse events and tolerability issues often leads to high level of treatment discontinuation. However, zanubrutinib adverse events associated with zanubrutinib appear to be more tolerable and manageable for patients than those associated with other BTK inhibitors.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Two separate economic models were developed to assess the cost of treating patients with zanubrutinib compared to alternative BTK inhibitors in patients with chronic lymphocytic leukaemia.

Patients with chronic lymphocytic leukaemia who have not previously received treatment

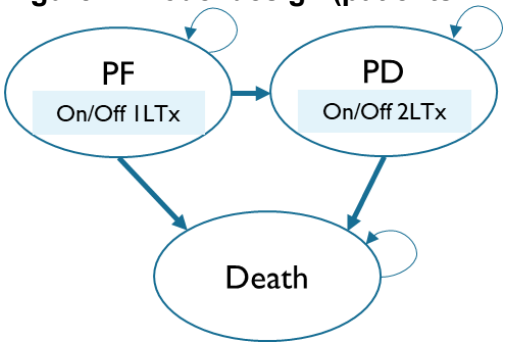
How the model reflects the condition

A model was developed to evaluate the cost saving of using zanubrutinib to treat patients who have not previously received treatment with:

- Acalabrutinib in patients with and without the 17p deletion or TP53 mutation high-risk genetic factors
- Ibrutinib in patients with the 17p deletion or TP53 mutation high-risk genetic factors

The model tracks patients as they move from being in a progression-free state to a progressed disease state or until death occurs (Figure 2Figure 1). The model calculates the cost of the initial treatment, one line of subsequent treatment (given at disease progression), disease management, adverse events, and end-of-life care.

Figure 2: Model design (patients who have not previously received treatment)



PD – Progressed disease; PF – Progression-free; 1LTx – First-line treatment; 2LTx – Second-line treatment.

Modelling how much a treatment extends life

As highlighted in Sections 3e and 3g, zanubrutinib delays the progression of the disease and improves survival. As the model focuses on the cost of treatment, it was assumed that zanubrutinib was equally as effective as acalabrutinib and ibrutinib. This assumption was supported by a number of analyses which supported the conclusion that zanubrutinib was at least as effective as acalabrutinib and ibrutinib. As such, this assumption is considered cautious and favoured acalabrutinib and ibrutinib. Please see Document B, Section B.3a.3 for more information.

Data from the SEQUOIA trial was projected over a 30-year time horizon and survival was capped by the survival observed in the general UK population. For patients receiving a subsequent treatment following progression on a BTK inhibitor, extrapolated data from the MURANO trial was used.[30] This was as all patients progressing on a BTK inhibitor were assumed to receive treatment with venetoclax-rituximab.

Modelling how much a treatment improves quality of life

Zanubrutinib is anticipated to have similar efficacy to acalabrutinib and ibrutinib, therefore, the health-related quality of life impact was equalised across all treatments in the model.

Modelling how the costs of treatment differ with the new treatment

The treatment acquisition cost and adverse event management costs associated with zanubrutinib were lower compared to both acalabrutinib and ibrutinib.

Uncertainty

The key uncertainties in the economic model relate to extrapolating the trial data. However, assuming equal effectiveness of all BTK inhibitors reduced the impact of this uncertainty.

Individual model inputs were varied to explore the sensitivity of the model to certain inputs and analyses were run where model parameters were varied according to set statistical distributions. In addition, the impact of alternative assumptions was tested.

Cost-effectiveness results

Over a lifetime time horizon, treatment with zanubrutinib resulted in lower costs for the National Health Service compared to ibrutinib and acalabrutinib in patients with chronic lymphocytic leukaemia who have not previously received treatment across all analyses.

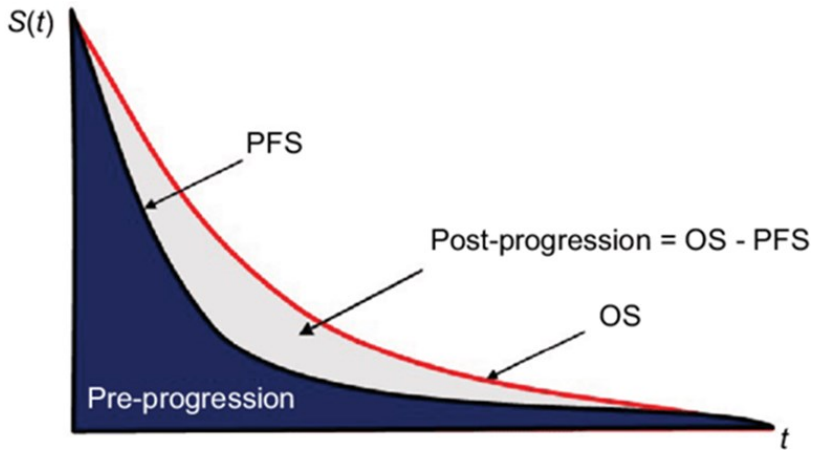
Relapsed/refractory chronic lymphocytic leukaemia

How the model reflects the condition

A model was developed to evaluate the cost saving of using zanubrutinib to treat patients with relapsed/refractory chronic lymphocytic leukaemia when compared to ibrutinib or acalabrutinib.

The model tracks patients as they move from being in a progression-free state to a progressed disease state or until death occurs (Figure 1Figure 1). The model calculates the cost of the initial treatment, one line of subsequent treatment (given at disease progression), disease management, adverse events, and end-of-life care.

Figure 3: Health state structure used in the economic model



PD – Progressed disease; PF – Progression-free.

Modelling how much a treatment extends life

As highlighted in Sections 3e and 3g, zanubrutinib delays the progression of the disease and improves survival. As the model focuses on the cost of treatment, it was assumed that zanubrutinib was equally as effective as acalabrutinib and ibrutinib. This assumption was supported by a number of analyses which supported the conclusion that zanubrutinib was at least as effective as acalabrutinib; although the ALPINE trial showed that zanubrutinib was superior to ibrutinib in preventing disease progression, in the model, it was assumed that zanubrutinib is equivalent to ibrutinib to reduce the level of uncertainty in the data extrapolations. As such, this assumption was cautious and favoured acalabrutinib and ibrutinib. Please see Document B, Section B.3b.3 for more information.

Data from the ALPINE trial were projected over a 30-year time horizon and survival was capped by the survival observed in the general UK population.

Modelling how much a treatment improves quality of life

Zanubrutinib is anticipated to have similar efficacy to acalabrutinib and ibrutinib, therefore, the health-related quality of life impact was equalised across all treatments in the model.

Modelling how the costs of treatment differ with the new treatment

The treatment acquisition cost and adverse event management costs associated with zanubrutinib were lower compared to both acalabrutinib and ibrutinib.

Uncertainty

The key uncertainties in the economic model relate to extrapolating the trial data. However, assuming equal effectiveness of all BTK inhibitors reduced the impact of this uncertainty.

Individual model inputs were varied to explore the sensitivity of the model to certain inputs and analyses were run where model parameters were varied according to set statistical distributions. In addition, the impact of alternative assumptions was tested.

Cost-effectiveness results

Over a lifetime time horizon, treatment with zanubrutinib resulted in lower costs for the National Health Service compared to ibrutinib and acalabrutinib in patients with relapsed/refractory chronic lymphocytic leukaemia across all analyses.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

As a next-generation BTK inhibitor, the ALPINE trial suggests that zanubrutinib reduces the increased risk of cardiac adverse events that are observed with ibrutinib and is more effective in keeping a patient's disease from progressing. As such, zanubrutinib may allow patients to receive an effective treatment for longer which is not captured in the economic models.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Due to the lack of clinical trial evidence available, patients who are suitable for treatment with chemo-immunotherapy (i.e. fludarabine-based and bendamustine-based therapy) and have not previously received treatment for their disease have not been included within the submission for zanubrutinib. As such, an equality issue arises in that younger and fitter

patients are denied access to a new treatment option that is efficacious, well-tolerated and improves patient choice, which is crucial given the differences in how chronic lymphocytic leukaemia can present in patients and in how patients respond to treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Information about chronic lymphocytic leukaemia :

- What is chronic lymphocytic leukaemia; https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/about
- Symptoms of chronic lymphocytic leukaemia: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/symptoms

Treatment guidelines:

- British Society for Haematology guidelines: https://onlinelibrary.wiley.com/doi/10.1111/bjh.18075

Information on zanubrutinib:

- Summary of product characteristics: https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf
- SEQUOIA: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00293-5/fulltext
- ALPINE: https://www.nejm.org/doi/full/10.1056/NEJMoa2211582

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

B-cell lymphoma 2: is a protein that helps control whether a cell lives or dies.

Bruton tyrosine kinase: a protein that plays a key role in the B-cell receptor signalling pathway which helps cancer cells grow and survive.

Overall survival: the length of time after starting treatment that a patient is alive.

Overall response rate: the proportion of patients who have a response to treatment i.e. the proportion of patients whose tumour disappears or is significantly reduced by a drug.

Progression-free survival: The length of time after starting treatment that a patient lives with a disease without it progressing.

Statistically significant: An outcome or result is it is not likely due to chance or other factor of interest.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. EMA. Brukinsa. *European Medicines Agency* 2022. at <https://www.ema.europa.eu/en/medicines/human/EPAR/brukinsa>
2. BRUKINSA 80 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/14001/smpc#gref>
3. BeiGene. *BeiGene. Press release. 2023*.
4. Bhayat F, Das-Gupta E, Smith C, *et al.* The incidence of and mortality from leukaemias in the UK: a general population-based study. *BMC Cancer* 2009. 9: 252.
5. Service NH. Overview Chronic lymphocytic leukaemia [Internet. 2019. at <https://www.nhs.uk/conditions/chronic-lymphocytic-leukaemia/>
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
[ID5078] Company responses to clarification letter v1.0	**V1.0**	**Yes**	**22/02/2023**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Literature searches

A1. Priority question. Appendix D, Table 1 (p. 2-3): The company reports one clinical effectiveness search strategy for three databases: Embase, MEDLINE and Embase Classic. Furthermore, the company reports searching the Cochrane Clinical Answers database (Appendix D, Table 2 (p. 5)). Please provide the individual search strategies in full and as run on each database searched and for each search conducted with the following additional information:

- URL and platform of the database used

- Name of the database (with time coverage)

- Date when the search was run

- Number of retrieved records per database

The Company would like to clarify that Embase (URL: http://www.embase.com/) is a comprehensive interface, which contains records from three databases:

- The Embase database: contains biomedical literature from 1974 to present.

- The MEDLINE database: covers journals from 1966 to present.
- Embase Classic: The Embase back file covering citations between 1947 and 1973.

It is only necessary to perform one search via the Embase interface to identify records across all three of these databases (Embase, MEDLINE, Embase Classic). The search strategy entered in the Embase interface is provided in Table 1 of Appendix D submitted alongside the Company submission. This table also contains the date when the search was conducted (1st July 2022) and the number of retrieved records from this interface.

A separate search strategy was used to perform a search via the Cochrane Library interface (URL: https://www.cochranelibrary.com/). The Cochrane Library interface contains records from both Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Clinical Answers. Cochrane Clinical Answers contains records added between 1995 to present and CENTRAL has no inception date. The search strategy used for the Cochrane Library interface is provided in Table 2 of Appendix D submitted alongside the Company submission. This table also contains the date when the search was conducted (1st July 2022) and the number of retrieved records for this database.

A2. Priority question. Appendix D, Table 1 (p. 3): The EAG notes that the reported clinical effectiveness strategy uses study type 'filters' for randomised controlled trials (RCTs) and observation *[sic]* studies. Please provide supportive information about the sensitivity and specificity of these filters, as well as bibliographic details of the filters' publications.

Filters developed by Scottish Intercollegiate Guidelines Network (SIGN) for RCTs and observational studies were used to inform the search strategies for the systematic literature review (SLR). The NICE methods guide refers to the York Centre for Reviews and Dissemination (CRD) guidelines for SLRs, which recommend search filters developed by SIGN for both RCTs and observational studies.[1–3] SIGN focuses on improving the quality of healthcare for patients in Scotland by reducing variation in practice and outcomes through the development of clinical guidelines containing recommendations for effective practice based on

current evidence. To aid the identification of relevant literature, SIGN developed database search filters based on systematic review evidence.

The filters sourced from SIGN are aimed at identifying higher quality evidence from large literature databases and were designed specifically for use in Embase and MEDLINE using index terms and free text.[4] Journals covered by Embase are indexed using Emtree, whilst the indexing of unique MEDLINE journals are mapped to Emtree terms. Therefore filters based on Emtree terminology/indexing can be used to search all Embase records, including those originally derived from MEDLINE.[5] A manual is available which outlines the key elements of the development process common to all SIGN guidelines:[6]

- SIGN. SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2015. (SIGN publication no. 50). [November 2015]. Available from URL: http://www.sign.ac.uk

A3. Appendix D, Table 6 (p. 7): Please provide justification that the range of sources used for the grey literature searches are: (a) exhaustive and comprehensive to locate relevant unpublished literature; and (b) provide a rationale for the selection of the time limits (2 years).

a) The range of sources used for the grey literature searches are considered exhaustive and comprehensive in locating relevant literature outside of the databases. Whilst the Embase or MEDLINE databases include a number of conferences from international meetings, there may be an initial delay in adding potentially relevant literature from recent conferences within the databases. As such, the grey literature search covered all recent conferences from international meetings considered potentially relevant to the treatment of chronic lymphocytic leukaemia (CLL), including major conferences in the field of oncology and/or haematology (see full list of included conferences below). The grey literature search also included additional searches of the websites of HTA bodies considered relevant to the UK (NICE and Scottish Medicines Consortium [SMC]) given that these may not be covered within the databases.

- Professional society for health economics and outcomes research (ISPOR): the leading global conference for health economics and outcomes research.
- American Society of Clinical Oncology (ASCO): includes presentations on the latest research in all areas of oncology.
- European Society for Medical Oncology (ESMO): a global oncology congress for clinicians, researchers, and healthcare industry representatives.
- American Society of Haematology (ASH): a global and comprehensive conference in the field of haematology.
- International Conference on Malignant Lymphoma (ICML): a key conference for the treatment of lymphoid neoplasms.
- European Haematology Association (EHA): a comprehensive conference for stakeholders in the field of haematology.

b) The short time limit is considered standard practice for grey literature searching and similar time limits have been accepted in previous NICE appraisals, including the appraisal for acalabrutinib for untreated and treated patients with CLL (TA689).[7] Additionally, any earlier conferences would have been captured in the database searches as the conferences listed above are covered within the Embase database which is inclusive of both recent and historic sources (see response to Question A1 for the exact time coverage).

Systematic Literature Review

A4. Appendix D, Section 1.3, Table 7 (p. 7): Please clarify the following regarding the inclusion criteria for the systematic literature review (SLR).

1. Population: To be eligible for inclusion in the SLR, what were the permitted age ranges that participants in eligible studies had to fall within?

The SLR restricted the population to “adult patients” which was defined as patients who are ≥18 years old. This is aligned with the MHRA/EMA licence for zanubrutinib for the treatment of patients with CLL and as per the population of interest within this NICE technology appraisal for zanubrutinib in CLL.[8,9]

2. Population: Were the company seeking papers for both the untreated chronic lymphocytic leukaemia (CLL) and relapsed or refractory (R/R) CLL? If so, what were the specific definitions of untreated or R/R CLL used to assess eligibility of a study?

The SLR did not restrict the population by using definitions for previously untreated and R/R CLL and no specific definitions were used to assess the eligibility of inclusion. Instead, the SLR was kept broad to cover all patients with CLL, which would inherently capture all patients with previously untreated and R/R CLL.

3. **Priority question. Population: Were there any exclusion criteria based on specific comorbidities? If so, what were they?**

The SLR did not restrict the population by comorbidity status with no specific exclusion criteria applied related to comorbidities.

4. Population: Were there any exclusion criteria based on specific medication use? If so, what were they?

The SLR did not restrict the population based on specific medication use with no specific exclusion criteria applied related to specific medication use.

5. Population: Regarding studies “with only a minority of patients being of interest”: (a) what was considered to be a “minority”; and (b) what was the rationale for excluding these studies?

Studies reporting a mixed population, i.e. populations covering CLL and alternative diseases, were excluded from the SLR if results were not reported specifically by disease type or if patients with CLL made up only a minority of the mixed population (defined as <50% of the total population). Results from mixed populations, containing only a minority of patients with CLL, would be heavily confounded by results from the other disease populations and generalising the results to CLL would introduce substantial uncertainty.

6. Population: Assuming that R/R CLL was eligible, were there any further exclusion criteria for participants based on prior lines of therapy? If so, what were they?

The SLR did not restrict the population by prior lines of therapy with no specific exclusion criteria applied related to prior lines of therapy.

7. Interventions/comparators: Were combinations of the listed comparator medications eligible for inclusion (e.g. bendamustine and rituximab [BR]) and, if yes, what were they?

The SLR was broad and did not restrict studies by intervention or comparator. Therefore, treatments beyond those recommended by NICE were captured in the SLR, including both monotherapies and combination therapies. For the purpose of the submission, the treatments included in the results write up for the SLR were restricted to only zanubrutinib and its comparators of interest within the NICE appraisal: ibrutinib and acalabrutinib monotherapy.

8. Interventions/comparators: Were any combination therapies alongside zanubrutinib eligible as a comparator (e.g. zanubrutinib and venetoclax) and, if yes, what were they?

Combination therapies alongside zanubrutinib were not considered within the SLR given that the focus of this NICE appraisal was zanubrutinib monotherapy as per the EMA and MHRA approval of zanubrutinib for the treatment of CLL.[8,9]

A5. Priority question. Appendix D, Section D.2 (p. 14): "As head-to-head data was available comparing zanubrutinib with ibrutinib in the ALPINE trial, an ITC was not required to inform this comparison. As such, references for RESONATE were not extracted." Please further elaborate on: (a) why an ITC would not have further informed the assessment of efficacy of zanubrutinib; and (b) why RESONATE was not used in this comparison.

ALPINE is an international, multi-centre, phase 3, RCT comparing zanubrutinib versus ibrutinib in patients with R/R CLL. As per the NICE methods, an ITC is only required in the absence of RCT data.[10] As direct head-to-head evidence is available from ALPINE, an ITC using RESONATE (pivotal trial for ibrutinib in R/R CLL) was

not considered necessary to inform the assessment of efficacy of zanubrutinib versus ibrutinib in patients with R/R CLL.

A6. Priority question. Appendix D Section 2.3 (p. 23) and Appendix N (p. 1-3): The EAG have a number of uncertainties around the matching adjusted indirect comparison (MAIC). These would be addressed if the protocol were provided. Please provide the full protocol for the MAIC.

Additional details pertaining to the MAIC methodology have been included within an updated version of Appendix N included in the zipped folder as part of the reference pack for this set of responses to clarification questions.

Clinical Trials

A7. Priority question. Section B1.1.1 (p. 10): Please provide the data of the quantitative survey of 30 UK-based CLL specialists, including:

1. **What questions were included in the survey**
2. **Descriptive results of the responses to each question.**

The EAG assumes this is covered by reference 8 in the company submission (p. 264). If so, please provide the data on file. If not, please clarify what extra information this relates to and provide the full report.

The quantitative survey report is included in the zipped folder as part of the reference pack for this set of responses to clarification questions. As this is data on file, the quantitative survey report should be treated as commercial in confidence (CIC).

A8. Priority question. Section B1.1.1 (p. 10): Please provide details of the five qualitative interviews that were undertaken with UK clinicians, including:

1. **How were the interviews double-blinded**

The interviews were double-blinded because:

- The interviews were conducted by a third-party vendor, and the interviewee was not aware of the Company who was conducting the research, or of the hypothetical product that was being discussed to determine its potential place in therapy in the UK market.

- The Company was not aware of which clinicians were being interviewed as their identity and profile was kept hidden from the Company.

2. The topic guide used by the interviewer

A discussion guide was provided in a Word document by the interviewer, covering topics including:

- **Context setting**: Gaining a high level of understanding of the respondent's experience with CLL.
- **Current process for patients diagnosed with CLL**: Understanding the respondent's process for making treatment decisions for CLL patients once diagnosed, and the challenges faced.
- **Potential unmet needs in the CLL**: Uncovering unmet needs in the CLL space.
- **Drivers of treatment choice and comparator landscape**: Assessing the drivers of treatment choice, the current treatment landscape for CLL, and perceptions of comparators.
- **Future of CLL treatment and target product profile (TPP) assessment**: Gauging awareness of new launches and innovation in the CLL space, and mapping where the opportunities are for new products coming to market.

3. What the selection criteria were for the experts

The selection criteria for the experts to be included in the interviews is listed below:

- CLL specialists (haematologist/oncologists) who had seen at least 20 patients in the past year.
- Had spent at least 70% in direct patient care.
- Were involved with diagnosing, managing and final treatment decisions for CLL patients.
- Were consultants or head of department/clinical leads.
- Between 3-30 years in practice.

4. How the experts were recruited and engaged

The experts were recruited from five different regions (London, South West, South East, North East and Scotland). They were invited to complete a 60-minute web-

assisted in-depth interview taking place on 15th August – 31st August 2022. Experts were offered an incentive of £300 for their participation in the research.

5. **A summary of the discussions with these experts**

The experts noted that BTKi and BCL2 therapy were the main treatments within CLL. For patients with previously untreated CLL, the experts agreed with the treatment pathway presented by the Company (as per Figure 1 in the Company submission), expressing uncertainty around using venetoclax as a monotherapy and using idelalisib as a primary treatment. In addition, the experts also confirmed that chemotherapy is rarely used due to the rise of other 'less invasive' treatments. For patients with R/R CLL, the experts agreed with the treatment pathway presented by the Company (as per Figure 1 in the Company submission), highlighting that the use of ibrutinib had been overtaken by acalabrutinib, and agreed with the 'treatment sequencing' concept. Acalabrutinib was deemed the preferred treatment in frailer or 'high-risk' patients and patients with comorbidities, with venetoclax-obinutuzumab was preferred in fit and younger patients given the risk of tumour lysis syndrome and gastrointestinal side effects.

The experts confirmed that a comparison with acalabrutinib would be very relevant as it is the standard BTKi used in clinical practice and BTKis would be the key comparators of interest for zanubrutinib.

The EAG assumes this is covered by reference 9 in the company submission (p. 264). If so, please provide the data on file. If not, please clarify what extra information this relates to and provide the full report.

A formal report was not developed, and key details are presented above.

A9. Priority question. Section B1.1.1 (p. 11): The following sentence is supported by reference 10 in the company submission: "In contrast, acalabrutinib would typically be prescribed for elderly patients or patients with comorbidities that would be unsuitable for FCR and BR therapy". However, reference 10 is incomplete in Section B.4. Additionally, reference 10 has been

used throughout the company submission for the qualitative interviews with clinicians. Please clarify the following:

1. **What justification was used to confirm prescribing practices for elderly patients or patients with comorbidities unsuitable for FCR and BR therapy?**
2. **Please provide the full bibliographic details for reference 10.**
3. **Does reference 10 also refer to qualitative interviews with clinicians and, if so, are these interviews the same as those reported in reference 9?**
4. **Please provide the data on file to support this reference.**

Reference 10 is a duplicate of reference 9 and is used to refer to the same set of 1:1 clinician interviews as per reference 9. Further details on these 1:1 clinician interviews are provided in response to question A8.

A10. Priority question. Section B1.1.1 (p. 11): Please provide a summary of the advisory board feedback from the meeting on 3rd November 2022. The EAG assume this is covered by reference 11 in the company submission (p. 264). If so, please provide the data on file. If not, please clarify what extra information this relates to and provide the full report.

The advisory board report is included in the zipped folder as part of the reference pack for this set of responses to clarification questions. As BeiGene data on file, the advisory board report should be treated as AIC.

A11. Section B1.4 (p. 35): Please provide details of the discussions held with patient organisations, including:

1. What patient organisations the company engaged with?

The Company engaged with relevant representatives from Leukaemia Care, Lymphoma Action and CLL Support Association.

2. How were patient organisations recruited and engaged?

The Company's initial desk research identified the CLL Support Association as a prominent patient-led support group that represented the voice of patients with CLL across the UK. Their website provided a range of information and support for patients, including scientific information on new treatment advances and they had

experience inputting into previous NICE submissions. An introductory meeting was arranged via their current Chair (details below) which led to their recommendation that in the context of NICE submissions, that the Company should also speak to representatives from Leukaemia Care and Lymphoma Action. They too had a shared interest in understanding new therapeutic advances and had in-house expertise and experience in providing patient perspectives into NICE appraisals. The CLL Support Association subsequently made the necessary introductions for the Company to meet with Leukaemia Care and Lymphoma Action.

3. When the company undertook these meetings?

The Company undertook these meetings between November 2022 and January 2023 – they consisted of three key virtual meetings to introduce the Company, the zanubrutinib data in CLL, and the overall strategy for the NICE submission.

4. A summary of the discussions from each patient organisation engagement, including how decisions surrounding exclusions of specific comparator therapies were elicited and reached.

Meeting 1

Date: 2 November 2022

Attendees: Representatives from BeiGene and CLL Support Association

This was an initial introductory meeting between BeiGene and CLL Support Association. The discussion was high level and centred on introducing BeiGene, the Company mission, the portfolio, and upcoming indication, CLL. Representatives from CLL Support Association introduced the charity and highlighted that they work very closely with Leukaemia Care and Lymphoma Action and that often these three patient organisations collaborate very closely and coordinate patient responses to input into NICE submissions. Following this meeting, the representative from CLL Support Association subsequently introduced BeiGene to relevant representatives from Leukaemia Care and Lymphoma Action to discuss the upcoming CLL NICE submission.

Meeting 2

Date: 20 December 2022

Attendees: Representatives from BeiGene, Leukaemia Care, Lymphoma Action and CLL Support Association

Following introductions, the Company gave an overview of the pivotal data in CLL and the NICE submission strategy and timelines, highlighting that the Company was seeking reimbursement in previously untreated 'unfit' and 'high-risk' patients, and previously treated CLL. This generated a strong negative reaction from all three patient representatives as they felt that the 'fit' population remains underserved and that all previous Company submissions had also neglected this population. They highlighted the limited treatment options available to these patients and that although venetoclax-obinutuzumab was available via the Cancer Drugs Fund (CDF), there were no guarantees that this would be recommended for routine commissioning, and even if it were, these patients deserve to have other treatment options available to them as not all patients can tolerate venetoclax-obinutuzumab and some may have a preference for a chronic treatment over fixed dose regimens. They also stressed the heterogeneity of CLL and the importance of a wide range of treatment options being made available. They urged the Company to re-consider this subgroup of patients as they are often unfairly 'left out' of NICE appraisals and miss out on getting access to novel treatments.

Meeting 3

Date: 10 January 2023

Attendees: Representatives from BeiGene, Leukaemia Care, Lymphoma Action and CLL Support Association

During this meeting, the Company thanked the patient organisations for their bold and honest feedback in the previous meeting. The Company highlighted that given the lack of trial data in this population, it would not be possible to submit an assessment in the 'fit' population at this stage. However, the Company acknowledged the equality issue this creates and that the Company would raise this in the Equality section of the NICE submission, as well as point NICE to relevant

evidence that might suggest that the effectiveness of zanubrutinib could be expected to be similar in this population as in the previously untreated 'unfit' or 'high-risk' populations. Patient organisations were satisfied with this approach and thanked the Company for listening and responding following their feedback.

A12. Section B1.4 (p. 35): Can the company please clarify who were the "patient and clinician groups" that highlighted "the inequality of BTKi being made available only in 'unfit' or 'high-risk' patients with untreated CLL"? If they were different to the groups mentioned previously in A7, A8, A9, A10, or A11, please provide details of the discussions held with these groups about these inequalities.

The patient groups and clinical experts are as per mentioned in Clarification Questions A7, A8, A9, A10 and A11. Please note, no specific clinician groups were liaised with, and the excerpt should read 'patient groups and clinical experts'.

A13. Priority question. Section B.2.2, Table 9 (p.39): Time to treatment failure (TTTF) is listed as an outcome for SEQUOIA but is not reported. Please provide the data on TTTF for SEQUOIA.

This was a typographical error in the write up of the submission and TTTF data is not available from SEQUOIA.

A14. Priority question. Section B.2.2, Table 9 (p.39): Please provide further justification as to why overall survival (OS) data from the ALPINE trial was used in the R/R CLL economic model but OS data from the SEQUOIA trial was not used in the treatment naïve CLL economic model when longer follow-up OS data was available for the SEQUOIA trial (Table 12 [p.45)] median follow-up for Cohort1 07 March 2022 data-cut: 36.1 months for Arm A, 35.4 months for Arm B) than the ALPINE trial (Table 31 [p. 78] median follow-up for 01 December 2021 data-cut: 24.34 months in the zanubrutinib arm and 23.82 months in the ibrutinib arm).

Despite SEQUOIA having longer follow-up for overall survival (OS) than ALPINE, the number of death events in SEQUOIA was considerably lower than in ALPINE. In SEQUOIA Cohort 1, only [redacted] deaths had occurred in the zanubrutinib arm and [redacted] in the BR arm after a median follow-up of 36.1 months and 35.4 months, respectively.

In Cohort 2, only [redacted] deaths were reported at a median follow-up time of 30.4 months. In contrast, [redacted] deaths had occurred in the zanubrutinib arm and [redacted] had occurred in the ibrutinib arm after a median follow-up of 24.9 and 24.6 months in ALPINE, respectively. As such, the OS data from ALPINE was deemed more reliable from which to extrapolate OS projections and these extrapolations were deemed sufficiently robust for use within the R/R economic model. In comparison, there were deemed to be too few death events in SEQUOIA to provide robust long-term extrapolations.

Furthermore, OS data was not used from SEQUOIA as more detailed subsequent treatment modelling was required in the CEM for patients with previously untreated CLL. In the UK, a BCL2i regimen is typically prescribed following progression on a front-line BTKi, with venetoclax-rituximab being considered the regimen of choice.[11,12] As the model assumes all patients would move to venetoclax-rituximab following progression on a BTKi, published data from MURANO was extrapolated and used to inform post-progression survival (PPS) in the model.[13] This approach reflects the treatment pathway more accurately and is consistent with the approach used in previous NICE appraisals for previously untreated CLL.[7] Feedback received from an advisory board conducted by the Company (03 November 2022) supported this approach.[11]

A15. Section B.2a.3.1 (p.41): It is stated that 65 participants in SEQUOIA were recruited from the UK. Please clarify the following:

1. How many of the 65 participants from the UK were included in each randomised arm of Cohort 1
2. How many of these 65 participants were recruited into Cohort 2.

Please note, a typographical error was included in the Company submission and 64 participants were enrolled in SEQUOIA from UK sites, of which:

- [redacted] were enrolled into Cohort 1 arm A (zanubrutinib)
- [redacted] were enrolled into Cohort 1 arm B (BR)
- [redacted] were enrolled into Cohort 2 (zanubrutinib)

The remaining [redacted] patients were enrolled in Cohort 3 arm D (zanubrutinib-venetoclax).

A16. Section B.2a.3.1 (p.41): Please clarify the following points regarding Cohort 1a:

1. Please provide reasoning for why Chinese participants in Cohort 1a were not generalisable to the English population.
2. Please provide the demographic information and baseline characteristics for Cohort 1a.
3. Please provide the outcome data for Cohort 1a.

Outcomes from Chinese participants in Cohort 1a of the SEQUOIA trial are not considered generalisable to the English population. Clinical disparities at diagnosis have been identified for patients with CLL across different ethnic groups. In particular, patients with CLL in China appear younger at diagnosis and display different mutational landscapes to patients with CLL in the UK and other Western countries.[14,15] Such differences in disease prognostics provided the incentive to monitor the efficacy of Chinese patients in a separate cohort of the SEQUOIA trial.

Differences in disease prognostics across Cohort 1 and Cohort 1a were demonstrated at baseline in the SEQUOIA trial (see Table 1 below). Patients in the Cohort 1a were younger on average (mean age of 63.5 years across both treatment arms in Cohort 1a vs 69.6 years in Cohort 1), with fewer patients above the age of 65 (58.8% in Cohort 1a vs 81.0% in Cohort 1). Furthermore, there were differences in background genotypes, with an increased frequency of IGHV mutation in Cohort 1a (62.5% in Cohort 1a vs 45.7% in Cohort 1).[16] The relative younger age and higher proportions of IGHV mutations in the observed in this study were consistent with what was reported in previous studies of Chinese patients with CLL/SLL.[17–19]

In addition, the median time from initial diagnosis of CLL/SLL to randomisation was shorter in Cohort 1a (6.24 months) compared to in Cohort 1 (30.03 months). This may be due to a later diagnosis with patients in Cohort 1a enrolling with later disease stage (Binet stage C: 60.3% in Cohort 1a versus 29.8% in Cohort 1) and higher tumour burden at diagnosis (cytopenia: 68.6% in Cohort 1a versus 44.1% in Cohort

1; bulky disease with LDi ≥ 5 cm: 38.4% in Cohort 1a versus 29.6% in Cohort 1; beta-2 microglobulin > 3.5 mg/L: 69.8% in Cohort 1a versus 55.5% in Cohort 1).

Since such factors are predictive of disease course and response to treatment, outcomes for Chinese participants cannot be considered generalisable to the English population. Clinical expert opinion highlighted that IGHV mutated patients are more likely to benefit from treatment with bendamustine-rituximab, and therefore the outcomes of patients from Cohort 1a will be heavily biased due to the high proportion of patients with this mutation.[20] Furthermore, feedback gathered from clinical experts at a UK advisory board (03 November 2022) conducted by the Company flagged that a recent clinical trial for ibrutinib, that was conducted in China, demonstrated a lower rate of response and higher rate of discontinuation in Chinese patients.[11,21]

Table 1: Baseline characteristics for Cohort 1 and Cohort 1a of the SEQUOIA trial

	Cohort 1		Cohort 1a	
	BR (N = 238)	Zanubrutinib (N = 241)	BR (N = 40)	Zanubrutinib (N = 40)
Cancer type, n (%)				
CLL	218 (91.6)	221 (91.7)	[redacted]	[redacted]
SLL	20 (8.4)	20 (8.3)	[redacted]	[redacted]
Age (years)				
Mean (SD)	69.35 (7.391)	69.82 (7.74)	[redacted]	[redacted]
Median	70	70	[redacted]	[redacted]
< 65 years	46 (19.3)	45 (18.7)	[redacted]	[redacted]
≥ 65 and < 75 years	139 (58.4)	133 (55.2)	[redacted]	[redacted]
≥ 75 years	53 (22.3)	63 (26.1)	[redacted]	[redacted]
Sex, n (%)				
Male	144 (60.5)	154 (63.9)	[redacted]	[redacted]
Female	94 (39.5)	87 (36.1)	[redacted]	[redacted]
White	206 (86.6)	221 (91.7)	[redacted]	[redacted]
Not Reported	21 (8.8)	9 (3.7)	[redacted]	[redacted]
Asian	9 (3.8)	4 (1.7)	[redacted]	[redacted]
Black or African American	1 (0.4)	4 (1.7)	[redacted]	[redacted]
Unknown	1 (0.4)	2 (0.8)	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)	[redacted]	[redacted]
Geographic Region, n (%)				

	Cohort 1		Cohort 1a	
	BR (N = 238)	Zanubrutinib (N = 241)	BR (N = 40)	Zanubrutinib (N = 40)
Europe	172 (72.3)	174 (72.2)	[redacted]	[redacted]
Asia Pacific[a]	38 (16.0)	33 (13.7)	[redacted]	[redacted]
North America	28 (11.8)	34 (14.1)	[redacted]	[redacted]
ECOG Performance Status, n (%)				
0	101 (42.4)	110 (45.6)	[redacted]	[redacted]
1	117 (49.2)	116 (48.1)	[redacted]	[redacted]
2	20 (8.4)	15 (6.2)	[redacted]	[redacted]
Time from initial diagnosis of CLL/SLL to randomisation (months)				
Mean (SD)	38.64 (38.60)	47.62 (49.67)	[redacted]	[redacted]
Median	28.67	31.28	[redacted]	[redacted]
Binet stage at study entry for CLL, n (%)				
A	28 (12.8)	30 (13.6)	[redacted]	[redacted]
B	124 (56.9)	126 (57.0)	[redacted]	[redacted]
C	66 (30.3)	65 (29.4)	[redacted]	[redacted]
Del17p, n (%)				
Yes	0 (0.0)	2 (0.8)*	[redacted]	[redacted]
No	238 (100.0)	239 (99.2)	[redacted]	[redacted]
TP53 mutation, n (%)				
Yes	13 (5.5)	15 (6.2)	NR	NR
No	210 (88.2)	217 (90.0)	NR	NR
Missing	15 (6.3)	9 (3.7)	NR	NR
Del17p or TP53 mutation, n (%)				
Yes	13 (5.5)	17 (7.1)	NR	NR
No	225 (94.5)	224 (92.9)	NR	NR
IGHV mutational status, n (%)				
Mutated	110 (46.2)	109 (45.2)	[redacted]	[redacted]
Unmutated	121 (50.8)	125 (51.9)	[redacted]	[redacted]
Undetermined	7 (3.0)	7 (2.9)	[redacted]	[redacted]
β_2 microglobulin, n (%)				
Mean (SD)	4.97 (6.94)	4.49 (3.19)	[redacted]	[redacted]
≤ 3.5 mg/L	98 (41.2)	99 (41.1)	[redacted]	[redacted]
> 3.5 mg/L	131 (55.0)	135 (56.0)	[redacted]	[redacted]

BR – Bendamustine-rituximab; CLL – chronic lymphocytic leukaemia; ECOG – Eastern Cooperative Oncology Group; IGHV – Immunoglobulin heavy chain variable region; PS – Performance status; SD – Standard deviation; SLL – Small lymphocytic lymphoma.
[a] Asia Pacific: Australia; New Zealand; Korea; China; and Taiwan, China.
*Inadvertent inclusion of these patients in Arm A.
Source: SEQUOIA CSR[16]

A17. Priority question. Please provide the clinical trial protocols and statistical analysis plans (SAPs) for both SEQUOIA and ALPINE as the EAG have several queries, listed below, which would be addressed with the trial protocols and SAPs for both trials.

1. Section B.2a.3.1, Table 10 (p.41-2): Please provide the following clarifications on the methods of the subgroups for SEQUOIA.
    a) Geographic region, lactate dehydrogenase (LDH), 13q deletion, complex karyotype and trisomy 12 are listed as pre-specified subgroups for SEQUOIA but not performed in Section B.2a.7 (Figure 12, p. 74). Please clarify the rationale behind this.
    b) Please provide subgroup analyses for IRC-assessed progression-free survival (PFS) for geographic region, LDH, 13q deletion, complex karyotype and trisomy 12 for SEQUOIA.

2. Section B.2b.3.1, Table 29 (p.75): Please provide the following clarifications on the methods of the subgroups for ALPINE:
    a) Patients with positive hepatitis B core antibody (HBcAB), time from initial diagnosis to randomisation and disease type are listed as pre-specified subgroups for ALPINE in Section B.2b.3.1 (Table 29, p. 75) but not performed in Section B.2b.7 (Figure 19, p. 99). Please clarify the rationale behind this.
    b) Please provide subgroup analyses for patients with positive HBcAB, time from initial diagnosis to randomisation and disease type for both overall response rate (ORR) by investigator (INV) and PFS by INV for ALPINE.
    c) Del 17p status and TP53 mutation status are listed as separate subgroups in the study design for ALPINE in Section B.2b.3.1 (Table 29, p. 75) but combined in the subgroup analyses in Section B.2b.7 (Figure 19, p. 99). What is the rationale behind this?
    d) Please provide separate subgroup analyses for del 17p status and TP53 mutation for ALPINE.
    e) Prior lines of therapy are presented as a subgroup analysis in Section B.2b.7 (Figure 19, p. 99) but is not stated as a prespecified subgroup in

Table 29 (Section B.2b.3.1, p. 76) or Table 33 (Section B.2b.4.2, p. 83). Was this subgroup added post-hoc and what was the rationale for including it?

3. A2. Section B.2a.3.2 (p. 44) and Section B.2b.3.2 (p. 77): Please clarify the following regarding the participant exclusion criteria for SEQUOIA and ALPINE.
   a) Please clarify how “clinically significant cardiovascular disease” was defined.
   b) Please clarify how a “severe or debilitating pulmonary disease” was defined.
   c) Please clarify if there was a limit on the number of comorbidities that participants could have.
   d) Please clarify if there was a limit on the number of medications that participants could be using.

4. Section B.2a.6.2 (p.62-3) and Section B.2b.6.2 (p.88-9): Were the sensitivity analyses performed in SEQUOIA and ALPINE pre-planned within the protocol or post-hoc analyses?

The clinical trial protocols and SAPs for SEQUOIA and ALPINE are included in the zipped folder as part of the reference pack for this set of responses to clarification questions. The protocols and SAPs are considered as data on file, and hence should be treated AIC.

A18. Section B.2a.3.4 (p. 47-50) and Section B.2b.3.4 (p. 79-80): Please clarify the following points regarding the participant demographics for SEQUOIA Cohort 1, SEQUOIA Cohort 2 and ALPINE.

1. **Priority question. How many comorbidities did the participants have in each arm of each trial on average?**

In SEQUOIA Cohort 1, comorbidities were reported in [redacted] patients in the zanubrutinib arm and [redacted] patients in the BR arm. In Cohort 2, comorbidities were reported in [redacted] patients. A full list of comorbidities can be found in

Table 14.3.5.1.1 for Cohort 1 and Table 14.3.5.1.3 for Cohort 2 in the SEQUOIA clinical study report (CSR). The most common comorbidities in SEQUOIA Cohort 1 and Cohort 2 are presented in Table 2.[16] The most frequently reported comorbidity was hypertension across all treatment arms.

Table 2: List of most common comorbidities in SEQUOIA

System Organ Class Preferred Term	Cohort 1		Cohort 2
	Arm A	Arm B	Arm C
	Zanubrutinib (N=241) N (%)	Bendamustine-rituximab (N=238) N (%)	Zanubrutinib (N=111) N (%)
Hypertension	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Benign prostatic hyperplasia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]

Source: SEQUOIA CSR[16]

In ALPINE, [redacted] patients in the zanubrutinib and [redacted] patients [redacted] in the ibrutinib arm had comorbidities. A full list of comorbidities can be found in Table 14.1.2.3 in the ALPINE CSR.[22] The most common comorbidities in ALPINE are presented in Table 3. The most frequently reported comorbidity was hypertension across both treatment arms.

Table 3: List of most common comorbidities in ALPINE

System Organ Class Preferred Term	Zanubrutinib (N=327) N (%)	Ibrutinib (N=325) N (%)
Hypertension	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Benign prostatic hyperplasia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

Source: ALPINE CSR[22]

2. How many other medications were the participants taking in each arm of each trial, on average?

A full list of concomitant medications in SEQUOIA Cohort 1 is listed in Table 14.3.5.3.1 in the SEQUIOA CSR and a full list of concomitant medications in SEQUOIA Cohort 2 is listed in Table 14.3.5.3.3.[16]

In SEQUOIA Cohort 1, almost all patients received one or more concomitant medication ([redacted] in the zanubrutinib arm; [redacted] in the BR arm) and the most common concomitant medications in both arms were:

- Antibacterial medications for systemic use ([redacted] patients in the zanubrutinib arm; [redacted] patients in the BR arm)
- Analgesics ([redacted] patients in the zanubrutinib arm; [redacted] patients in the BR arm)
- Antigout preparations ([redacted] patients in the zanubrutinib arm; [redacted] patients in the BR arm)
- Corticosteroids for systemic use ([redacted] patients in the zanubrutinib arm; [redacted] patients in the BR arm).

In SEQUOIA Cohort 2, almost all patients received one or more concomitant medication ([redacted] in the zanubrutinib arm) and the most common concomitant medications were:

- Antibacterial for systemic use ([redacted] patients)
- Analgesics ([redacted] patients)
- Agents acting on the renin-angiotensin system ([redacted] patients)
- Antigout preparations ([redacted] patients)
- Antithrombotic agents ([redacted] patients).

A full list of concomitant medications in ALPINE are listed in Table 14.1.2.6 in the ALPINE CSR.[22] In ALPINE, almost all patients in the safety analysis set received one or more concomitant medication ([redacted] in the zanubrutinib arm; [redacted] in the ibrutinib arm). The most common concomitant medications in both arms were:

- Antibacterial for systemic use ([redacted] patients in the zanubrutinib arm; [redacted] patients in the ibrutinib arm)
- Antigout preparations ([redacted] patients in the zanubrutinib arm; [redacted] patients in the ibrutinib arm)
- Antivirals for systemic use ([redacted] patients in the zanubrutinib arm; [redacted] patients in the ibrutinib arm).

3. **Priority question. For ALPINE, how many prior lines of therapy had the participants been previously treated with?**

The number of prior lines of therapy received in ALPINE is presented in Table 4. The majority of patients had only received one prior line of therapy before initiation of the study treatment.

Table 4: Participants prior lines of therapy in ALPINE

Number of prior lines of systemic therapy, n (%)	Zanubrutinib (N=327)	Ibrutinib (N=325)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
≥6	[redacted]	[redacted]

Source: ALPINE CSR[22]

4. For ALPINE, what were the prior lines of therapy that the participants had previously been treated with?

In ALPINE, the most commonly reported prior line of therapy that the participants had received were: fludarabine-cyclophosphamide-rituximab (FCR), venetoclax-based regimens (including venetoclax-rituximab and venetoclax-obinutuzumab), chlorambucil-based regimens (including chlorambucil-obinutuzumab, chlorambucil-prednisone and chlorambucil-rituximab), and bendamustine-based regimens (including bendamustine-rituximab). The full list of other prior lines of therapy that participants received are listed in Table 14.1.2.4 in the ALPINE CSR.[22]

5. For ALPINE, please clarify how many participants in each arm had an ECOG score of 0 and an ECOG score of 1 separately.

In the zanubrutinib arm, [redacted] participants had an ECOG performance score of 0 and [redacted] of patients had an ECOG score of 1. In the ibrutinib arm, [redacted] participants had an ECOG score of 0 and [redacted] had an ECOG score of 1.[22]

A19. Section B.2a.5 (p. 57-8) and Section B.2b.5 (p. 84-5): Please clarify the following regarding the critical appraisal of SEQUOIA and ALPINE:

1. Which tool was used to perform the critical appraisals?
2. The method for undertaking the critical appraisals.
3. Provide further justification for all risk of bias judgements made in each domain.

The critical appraisal of the SEQUOIA and ALPINE trials was performed using the criteria for the assessment of risk of bias and generalisability listed in Section 2.5.2. of the NICE STA user guide.[23,24] The critical appraisal assessments for SEQUOIA Cohort 1, SEQUOIA Cohort 2 and ALPINE are provided with further justification in Table 5, Table 6 and Table 7, respectively. Cohort 1 of SEQUOIA and ALPINE use the checklist for RCT assessment, while Cohort 2 of SEQUOIA uses the non-RCT assessment checklist. The overall study design features for both SEQUOIA and ALPINE were also agreed upon by the EMA during the European public assessment report (EPAR); the EMA did not raise any concerns with the design of the trials and

further noted that the totality of evidence supports the use of zanubrutinib in both previously untreated and relapsed/refractory patients.

Table 5: Quality assessment results for SEQUOIA Cohort 1

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomised 1:1 using Interactive Response Technology. Randomisation was stratified by a number of factors to reduce imbalance between treatment groups. These techniques minimised the potential for selection bias.	Yes
Was the concealment of treatment allocation adequate?	This was an open-label study. Treatment with zanubrutinib and treatment with BR was open-label; however, the IRC for response assessment was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were the groups similar at the outset of the study in terms of prognostic factors	Baseline demographic and disease characteristics were similar between groups in terms of prognostic factors, with only small differences seen in race and age. See Section B.2a.3.4 of the Company Submission for more detail.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	This was an open-label study. Patients and investigators were not masked to treatment. The IRC for response assessment was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were there any unexpected imbalances in dropouts between groups?	There were no unexpected imbalances in dropouts between groups. See Section B.2a.4.3 of the Company Submission for more detail.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR, therefore there is no evidence to suggest authors measured further outcomes.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the analysis reported ITT analysis, this was appropriate to preserve randomisation and minimise the risk of bias. Appropriate methods were used to account for missing data; missing data were not imputed unless otherwise specified.	Yes

CSR – Clinical study report; IRC – Independent review committee; NA – not applicable.

Table 6: Quality assessment results for SEQUOIA Cohort 2

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was the cohort recruited in an acceptable way?	Patients were recruited from 160 study locations and allocated to Cohort 2 dependent on mutation status.	Yes
Was the exposure accurately measured to minimise bias?	Extent of exposure, including treatment duration and dose reduction was measured to minimise bias. See Section B.2a.10.1 of the Company Submission for more detail.	Yes
Was the outcome accurately measured to minimise bias?	Outcomes were accurately measured to minimise bias. See Section B.2a.3.3 of the Company Submission for the definition of each outcome measure.	Yes
Have the authors identified all important confounding factors?	All important confounding factors were considered within pre-planned subgroup analyses. See Section B.2a.6 of the Company Submission for more detail.	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes, the authors have considered the impact of potential confiding factors in the analysis, including the potential impact of COVID-19.	Yes
Was the follow-up of patients complete?	See Section B.2a.6 of Company Submission.	Yes
How precise (for example, in terms of confidence interval and p values) are the results?	See Section B.2a.6 of Company Submission.	Yes

CSR – Clinical study report; IRC – Independent review committee; NA – not applicable.

Table 7: Quality assessment results for ALPINE

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomised 1:1 using Interactive Response Technology. Randomisation was stratified by a number of factors to reduce imbalance between treatment groups. These techniques minimised the potential for selection bias.	Yes
Was the concealment of treatment allocation adequate?	This was an open-label study. Treatment with zanubrutinib and treatment with ibrutinib was open-label; however, the IRC for response assessment was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were the groups similar at the outset of the study in terms of prognostic factors	Baseline demographic and disease characteristics were similar between groups in terms of prognostic factors, with only small differences were seen in sex and age. See Section B.2b.3.4 of the Company Submission for more detail.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	This was an open-label study. Patients and investigators were not masked to treatment. The IRC was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were there any unexpected imbalances in dropouts between groups?	There were no unexpected imbalances in dropouts between groups. See Section B.2b.4.3 Participant flow.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR, therefore there is no evidence to suggest authors measured further outcomes.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the analysis reported ITT analysis, this was appropriate to preserve randomisation and minimise the risk of bias. Appropriate methods were used to account for missing data; missing data were not imputed unless otherwise specified.	Yes

CSR – clinical study report; IRC – independent review committee; NA – not applicable.

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Priority question. Appendix D, Tables 1, 3, 4 and 5: The company has reported the cost-effectiveness search alongside the clinical effectiveness search in Table 1 (p. 3) and the additional searches in other databases in Tables 3, 4 and 5 (p. 6).

1. **Please provide the search strategy for cost-effectiveness, health related quality of life (HRQoL), costs and resource use for the three databases, Embase, MEDLINE and Embase Classic, separately to the clinical effectiveness search.**

2. **Please provide individual search strategies for all cost-effectiveness data in full and as run on the reported databases (Embase, MEDLINE, Embase Classic, EuroQol, NHS EED and NHS HTA) with the following additional information:**

   - URL and platform of the database used

   - Name of the database (with time coverage)

   - Date when the search was run

   - Number of retrieved records per database

As highlighted in Appendix D of the Company submission, a single integrated SLR was conducted to identify existing clinical, cost-effectiveness, health-related quality-of-life (HRQoL) and cost and resource use studies conducted in CLL. As noted in the Company response to Clarification Question A1, the Embase interface (URL: http://www.embase.com/) is able to identify records across all three of these databases (Embase, MEDLINE, Embase Classic). The search strategies used for cost-effectiveness, HRQoL, and cost and resource studies for the Embase interface can be found in Table 1 of Appendix D submitted alongside the Company submission. This table also contains the date when the search was conducted (1st July 2022) and the number of retrieved records from this interface.

The individual search strategies used to search the ScHARRHUD (URL: https://www.scharrhud.org/index.php?recordsN1&m=search), EuroQol (URL: https://euroqol.org/publications/search-for-eq-5d-documents/) and NHS HTA and EED (URL: https://www.crd.york.ac.uk/CRDWeb/) databases can be found in Tables 3 – 5 of Appendix D submitted alongside the Company submission. These tables also contain the date when the search was conducted (1st July 2022) and the number of retrieved records for each database.

The ScHARRHUD database contains records added from 2010 to present. The NHS EED database contain records added between 1994 and March 2015 only and the HTA database contains records up until 2018. EuroQol contains records from 1970 to present. The time coverage of the three component databases can be found in the Company response to Clarification Question A1.

B2. Priority question. Appendix D, Table 1 (p.3-4): The EAG notes that the reported cost-effectiveness, HRQoL and cost and resource use strategy uses study type 'filters' for economic studies. Please provide supportive information about the sensitivity and specificity of this filter and provide the bibliographic details of the filter publication?

Filters developed by SIGN for cost-effectiveness, HRQoL and cost and resource use studies were used. Further details regarding the SIGN filters can be found in the Company response to Clarification Question A2.

B3. Priority question. Appendix D, Table 1 (p.4): The EAG notes that the reported cost-effectiveness, HRQoL and cost and resource use strategy uses study type 'filters' for Quality of Life studies. The company has provided a URL link to a conference abstract that is missing relevant information on the sensitivity and specificity of this filter, the actual filter and the bibliographic details of its publication. Please provide relevant bibliographic references for the HSuV filters used.

The URL provided by the Company in Appendix D, Table 1 aligns with the most sensitive health state utility values (HSuV) filter designed by York Health Economic Consortium. Three filters were sampled in an identification of systematic reviews and all three filters performed at over 90% sensitivity with varying precision.[25]

Bibliographic details of the URL are listed below, and the search filters can be found within the associated poster, also listed below.

- Arber M, Garcia S, Veale T, Glanville J. Sensitivity of a search filter designed to identify studies reporting health state utility values. In: Filtering the information overload for better decisions. Abstracts of the 23rd Cochrane Colloquium; 2015 3-7 Oct; Vienna, Austria. John Wiley & Sons; 2015.[26]

- Arber et al. Sensitivity of a Search Filter Designed to Identify Studies Reporting Health State Utility Values. York Health Economics Consortium. University of York. 2015.[25]

B4. Appendix D (p. 2): Please clarify which HTA database has been used and provide details as per point B1 of this letter

The NHS HTA and EED (URL: https://www.crd.york.ac.uk/CRDWeb/) database via the University of York website was used. Table 5 of Appendix D submitted alongside the Company submission displays the search strategy used for this database, alongside the date of the search and the number of hits retrieved. The HTA database search was also supplemented with grey searches of the websites of HTA bodies considered relevant to the UK (NICE and SMC).

B5. Section B3 (p. 163): Please provide justification for relying on the main SLR and not conducting further targeted literature reviews for costs and HRQoL on the MEDLINE and EMBASE databases.

The main SLR was an extensive search of multiple databases which are detailed in Appendix D Section D1.2 Search strategy. A targeted literature review within the same databases as the SLR was not deemed necessary in addition to the searches that had already been carried out for costs and HRQoL as all relevant literature should have been identified within the SLR and grey literature search. Furthermore, this approach is consistent with the NICE methods guide, which states that resource use, cost and HRQoL data should be identified systematically.[10]

Economic analysis

B6. Priority question. Section B.2.9 and B.3a.2: The company state that, based on their findings from the MAIC, "zanubrutinib is at least non-inferior to

acalabrutinib" and "it is clinically plausible to conclude that zanubrutinib will be at least non-inferior to ibrutinib," hence they undertook a cost-minimisation analysis (CMA) (p. 166). However, evidence of non-inferiority needs to be demonstrated for all outcomes of interest. This includes placing the outcome data reported in the context of justified minimally important differences. Please provide this evidence of non-inferiority for the following outcomes:

- **OS**
- **Time to treatment failure**
- **Grade ≥ 3 adverse events**
- **HRQoL (EORTC QLQ-C30 and EQ-5D-5L utility scores)**

In oncology, PFS is the most widely and consistently reported endpoint in clinical trials and, therefore, is often the key determinant in comparing the effectiveness of different treatments. Across the MAICs and clinical trials, zanubrutinib offers at least non-inferior PFS to acalabrutinib and ibrutinib in both the previously untreated and R/R CLL settings as described in Section B.2.9 of the Company submission. Clinical experts in attendance at an advisory board conducted by the Company (03 November 2022) supported the notion that zanubrutinib would be at least non-inferior to the other BTKi treatment options.[11]

OS

The Company conducted three MAICs, a naïve comparison, and leveraged direct head-to-head data from ALPINE to assess differences in OS between treatments, with all evidence supporting the conclusion than zanubrutinib was at least non-inferior to both acalabrutinib and ibrutinib:

- Comparison with acalabrutinib in 'unfit' and 'high-risk' patients (see Document B, Section B.2.9.1 for further details): A MAIC was conducted to compare the efficacy of zanubrutinib (SEQUOIA, pooled arm A and arm C) and acalabrutinib (ELEVATE-TN) in patients with previously untreated CLL who are unsuitable for FCR and BR therapy, irrespective of the presence of a 17p deletion and/or TP53 mutation. The MAIC demonstrated that

there was no statistically significant difference in OS between zanubrutinib and acalabrutinib, with hazard ratios of [redacted] (95% CI, [redacted]) in Model 1 and [redacted] (95% CI, [redacted]) in Model 2. Feedback received from an advisory board conducted by the Company (03 November 2022) noted that the low number of deaths in SEQUOIA leads to high uncertainty in the relative OS estimates. Furthermore, the experts also noted that the unadjusted and adjusted KMs for PFS and OS were similar for zanubrutinib and acalabrutinib, supporting the non-inferiority of zanubrutinib to acalabrutinib.[11]

- Comparison with ibrutinib in 'high-risk' patients (see Document B, Section 3a.3.4.2 for further details): A naïve comparison was conducted to compare the efficacy of zanubrutinib versus ibrutinib in patients with previously untreated CLL comparing 'high-risk' specific data from Mato et al. (2018) with Cohort 2 (arm C) of SEQUOIA.[27] The comparison demonstrated a statistically significant improvement in OS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted]).

- Comparison with acalabrutinib in R/R CLL patients (see Document B, Sections B.2.9.2 and B.2.9.3 for further details): Two MAICs were conducted both of which demonstrated that zanubrutinib is at least non-inferior to acalabrutinib in patients with R/R CLL – one conducted using ELEVATE-RR and one using ASCEND.[28,29] The MAIC using ELEVATE-RR demonstrated that there was no statistically significant difference in OS between zanubrutinib and acalabrutinib, with hazard ratios of [redacted] (95% CI, [redacted]) and [redacted] (95% CI, [redacted]) reported in Model 1 and 2, respectively. Similarly, the MAIC using ASCEND demonstrated that there was no statistically significant difference in OS between zanubrutinib and acalabrutinib, with hazard ratios of [redacted] (95% CI, [redacted]) and [redacted] (95% CI, [redacted]) reported in Model 1 and 2, respectively. No statistically significant difference was observed for OS between zanubrutinib and acalabrutinib across the two MAICs. Feedback received from an advisory board conducted by the Company (03 November 2022) noted that the similarity between the unadjusted and adjusted PFS and OS

KMs for zanubrutinib and acalabrutinib supported the non-inferiority of zanubrutinib to acalabrutinib in patients with R/R CLL.[11]

- Comparison with ibrutinib in R/R CLL patients: Despite being immature, head-to-head data from ALPINE demonstrated that zanubrutinib was associated with a [redacted] reduction in the risk of death compared when compared to ibrutinib [redacted], as per the data cut off (DCO) on 01 December 2021.[22] Late breaking data from DCO 08 August 2022, with a median follow-up of 29.6 months, demonstrated that the difference in number of deaths between zanubrutinib and ibrutinib further increased, further highlighting the improved outcomes on zanubrutinib. Furthermore, the hazard ratio (HR:0.76; 95% CI: 0.51, 1.11) is lower within a narrower confidence interval compared to the 2021 DCO, suggesting that a statistically significantly improvement in OS may be demonstrated with more mature data.[30]

Time to treatment failure

It was not possible to make robust comparisons of TTTF across trials, as the endpoint was not collected in SEQUOIA and TTTF data were not consistently available for comparator treatments of interest.

TTTF in ALPINE is defined as time from randomisation to discontinuation of study drug due to any reason. At median follow-up of 25.1 months, compared to ibrutinib, treatment with zanubrutinib was associated with a statistically significant [redacted] % reduction in TTTF (HR:[redacted]; 95% CI: [redacted]; p<[redacted]).[22] Furthermore, treatment with zanubrutinib was associated with a statistically significant [redacted] % reduction in the risk of INV-assessed disease progression or death when compared to treatment with ibrutinib (HR: [redacted]; 95% CI[redacted]; p=[redacted] [superiority 2-sided p-value]) at the 01 December 2021 data cut-off. As all three BTKis are licensed for treatment until progression, the conclusions drawn from the PFS comparisons (head-to-head data from ALPINE and via the MAICs versus acalabrutinib) are highly generalisable to the TTTF outcome. As such, it is clinically plausible that if an indirect treatment comparison was feasible on TTTF versus acalabrutinib (R/R and

previously untreated patients) and ibrutinib (previously untreated 'high-risk' patients) zanubrutinib would demonstrate at least non-inferiority to the other BTKis.

Grade ≥ 3 adverse events

Zanubrutinib is tolerable and safe in the treatment of patients with previously untreated and R/R CLL with an improved safety profile compared to first-generation BTKis.

The SEQUOIA trial reported low atrial fibrillation rates for zanubrutinib, occurring in 8 (3.3%) patients in Cohort 1 and 5 (4.5%) patients in Cohort 2, these rates were similar to those reported in the BR arm (2.6%). In comparison, an increased rate of atrial fibrillation was reported with ibrutinib versus CIT treatment in randomised studies.[31,32] In the ALPINE trial, the rate of atrial fibrillation or flutter, a key secondary endpoint, was statistically significantly lower in the zanubrutinib arm (4.6%) compared to ibrutinib (12.0%). No sudden deaths with zanubrutinib were reported in either trial. In ALPINE there were no deaths due to cardiac disorders with zanubrutinib whereas five patients treated with ibrutinib died due to a cardiac adverse events (AE), all of which occurred ≤ 30 days after the last dose of study drug.

Whilst a formal comparison has not been conducted between zanubrutinib and acalabrutinib, reduced inhibition of off-target kinases with zanubrutinib might lead to reduced risk of cardiac AEs and tolerability issues observed with ibrutinib and acalabrutinib leading to discontinuation of treatment, which is not captured in the model. Results at a median follow-up time of 12 months from an ongoing, phase 2, single-arm trial evaluating the efficacy of zanubrutinib in patients previously treated for B-cell malignancies who became intolerant to ibrutinib, acalabrutinib, or both, demonstrated that the majority of intolerance events (70% for ibrutinib and 83% for acalabrutinib) did not recur with zanubrutinib, and that no events recurred with higher severity.[33] Furthermore, AEs associated with zanubrutinib seemed more tolerable and manageable for patients than those associated with other BTK inhibitors.[33]

When assessing the impact of AEs by relaxing the non-inferiority assumption and incorporating Grade ≥3 AE from the clinical trials into the model, zanubrutinib was associated with fewer AE costs and a lower AE-related disutility. The aggregate

costs and disutilities associated with Grade ≥3 AE in the previously untreated model and the R/R model are presented in Table 8 and Table 9, respectively. These results suggest that zanubrutinib has at least a non-inferior safety profile to acalabrutinib and ibrutinib and assuming equivalence of AE burden in the models is conservative.

Table 8: Aggregated costs and disutilities of Grade ≥3 AE in the treatment naïve CLL population

	Costs	Disutilities
Zanubrutinib	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]

AE – Adverse event; CLL – Chronic lymphocytic leukaemia

Table 9: Aggregated costs and disutilities of Grade ≥3 AE in the R/R CLL population

	Costs	Disutilities
Zanubrutinib	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; R/R – Relapsed or Refractory

HRQoL

It was not possible to make robust comparisons of HRQoL data, as HRQoL data were not consistently available for comparator treatments of interest.

Both the treatment naïve and R/R CLL models use non-treatment specific health state utility values. The Company does not claim that zanubrutinib improves patients' HRQoL, however, when assessing the impact of HRQoL by relaxing the non-inferiority assumption, zanubrutinib was more effective and less costly than acalabrutinib and ibrutinib in the treatment naïve model (see Document B Sections B.3a.11.3). Furthermore, when considering the mean incremental costs and QALYs over the four cost-utility scenarios versus acalabrutinib, zanubrutinib was more effective and less costly and hence dominates acalabrutinib in the R/R population. In addition, zanubrutinib dominated ibrutinib when relaxing the non-inferiority assumption in the R/R population.

The EORTC QLQ-C30 and EQ-5D instruments were used in ALPINE to measure patient reported outcomes. When using the EORTC QLQ-C30 instrument, the mean

changes from baseline of key patient reported endpoints showed greater improvements in the zanubrutinib arm compared with the ibrutinib arm, with the exception of pain, which showed similar improvement between the arms. When using the EQ-5D-5L instrument, mean change from baseline in the visual analogue scale showed a consistently better improvement (Mean [SD]) in patients in the zanubrutinib arm compared with patients in the ibrutinib arm at Cycle 7 (Zanubrutinib: [redacted]; Ibrutinib: [redacted]) and Cycle 13 (Zanubrutinib: [redacted]; Ibrutinib: [redacted]).[22] As all three BTKis are licensed for treatment until progression, the conclusions drawn from the PFS comparisons are highly generalisable to the HRQoL outcome. As such it is clinically plausible that if an indirect treatment comparison was feasible on HRQoL versus acalabrutinib (R/R and previously untreated patients) and ibrutinib (previously untreated 'high-risk' patients) zanubrutinib would demonstrate at least non-inferiority to other BTKis.

Additionally, assuming non-inferiority for HRQoL across all treatments was accepted during the appraisal for acalabrutinib for previously untreated and R/R patients with CLL (TA689).[7]

Clinical parameters

B7. Priority question. Section B.3a.3.1 (p. 175): It is stated that the best fitted distribution involved assessment of clinical plausibility leveraging clinical expert opinion. Similar statements regarding the use of expert opinion are used elsewhere in the remaining sub-sections of the document (e.g. use of general population mortality for pre-progression survival [PrePS], p. 180); base case curve selection for time to progression (TTP) and PrePS (Section B.3a.3.2.3, p. 180); and treatment sequencing approach post progression [Section B.3a.3.3, p. 183]). The company rely on several data sources that are not available to the EAG. These are cited within the company submission (Section B4) as references 7-11. Please provide these data files; the EAG have also requested these data files in clarification points A7, A8, A9, and A10.

Please see Company responses to Clarification Questions A7, A8, A9 and A10, with the clinical advisory board being the key reference of interest (A10). All submitted references are considered as data on file, and as such should be treated as AIC.

B8. Section B.3a.3.2.2 (p. 178): “A low number of pre-progression death events were observed across both Cohort 1 (arm A and arm B) and Cohort 2 (arm C) of the SEQUOIA trial, and as such, data across all three arms were used to inform the PrePS extrapolation.”

1. Please detail the methodology used to pool the data across both cohorts in the model.
2. Given the potential risk of bias, please comment on the potential for bias this may cause, especially given data from the comparator arm is also included.
3. Please elaborate on why these potential biases are not considered sufficient to prevent pooling of these data.

Pooled PrePS was derived by taking a simple average of the individually extrapolated PrePS projections for zanubrutinib and BR, which were each constrained by the competing risk of death in the general population.

The low number of pre-progression deaths in the SEQUOIA trial ([redacted] in the zanubrutinib arm and [redacted] in the BR arm), which may be further biased by COVID-related deaths occurring in the zanubrutinib arm, were neither sufficient to allow for long-term projection nor to inform meaningful treatment effect associated with zanubrutinib compared to BR. On this basis, the approach of pooling the data was taken to make the best use of the available trial data, to ensure face validity and to mitigate the risk of bias caused by extrapolating data with few events.

Moreover, given that COVID-related deaths occurred in the zanubrutinib arm and the fact that more pre-progression deaths were observed in the BR arm, a pooled PrePS approach can be considered as conservative. If COVID-related events were excluded and the zanubrutinib PrePS was considered alone, the extrapolation of PrePS would be more optimistic in comparison to the pooled estimate of PrePS. As PrePS is capped by general population mortality within the model, the choice of PrePS source (extrapolated zanubrutinib PrePS alone or combined with the PrePS from BR arm) is not a key driver of cost-effectiveness.

B9. Section B.3a.3.3 (p.183): Please provide further justification on why the MURANO study was deemed the most appropriate data source to inform post-progression survival (PPS) and the duration of subsequent treatments in the model.

As highlighted within the anticipated treatment pathway presented in the Company submission (Document A, Figure 1), following disease progression on initial treatment, patients move onto subsequent therapies that are determined by the first-line treatment received. Based on the 2022 BSH guidelines and clinical expert opinion, a BCL2i regimen is typically recommended following progression on a front-line BTKi, regardless of which BTKi is initially prescribed.[11] Clinical experts advised that venetoclax-rituximab is considered the venetoclax regimen of choice.

The MURANO study was identified in the SLR investigating treatments in patients with previously untreated and R/R CLL. MURANO was a randomised, open-label, phase III study that evaluated the efficacy of venetoclax-rituximab (venetoclax up to 2 years; rituximab for six 28-day cycles) compared to BR (both bendamustine and rituximab for six 28-day cycles) in 389 previously treated patients with R/R CLL. MURANO is the key pivotal phase III trial for venetoclax-rituximab, offering the most robust data possible for the treatment regimen. As such, MURANO was deemed the most appropriate data source to inform PPS and the second-line PFS (i.e. the duration of subsequent treatment) within the model to align with the anticipated treatment pathway in the UK. The choice of the MURANO study to inform post-progression modelling was validated by UK clinical experts in attendance at an advisory board (03 November 2022) held by the Company and was accepted by NICE in a recent appraisal in CLL.[7,11]

B10. Section B.3a.3.3.1 (p. 184): “As the exponential distribution provided the best statistical fit and there is no strong evidence of an increasing risk before general population mortality is applied, it was selected to inform the base case.” Please provide further justification on how the evidence was assessed as not being “strong”?

During the appraisal for acalabrutinib for untreated and treated patients with CLL (TA689), clinical experts in attendance at the Appraisal Committee Meeting agreed with the use of the exponential distribution to inform PPS modelling highlighting the

lack of “strong” evidence of an increasing risk before general population mortality is applied at ~90 months.[7] Similarly, as the same MURANO OS data source is used to model PPS in the Company’s submission for zanubrutinib, the clinical opinion as per TA689 is deemed relevant to support modelling a constant risk of death.

As highlighted in Section B. 3a.3.3.1 of Document B, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best-fitting curve (Company Submission, Document B, Table 74). The PPS curve is not a large driver of the cost-effectiveness as equal efficacy is assumed in the model and PPS is constrained by general population mortality for the duration of the time horizon.

B11. Section B.3a.3.4.1 (p. 189): “The MAICs conducted using ELEVATE-RR and ASCEND contained a high proportion of patients with a 17p deletion or TP53 mutation (~40% each), these analyses are deemed highly relevant as a proxy for previously untreated patients with 17p deletion and/or TP53 mutation”. Please provide further justification to support the assumption that these patients were a good proxy for previously untreated ‘high-risk’ patients?

NICE assessed acalabrutinib in TA689 and ibrutinib in TA429 for the treatment of previously untreated and R/R patients with CLL using evidence from the ASCEND and RESONATE trials, respectively.[7,34] Both ASCEND and RESONATE were conducted in patients with R/R CLL and did not contain any evidence of efficacy in the first-line setting. However, the respective Committees deemed this data highly relevant to decision making in the first-line setting which led to a positive recommendation by NICE for both treatments in previously untreated patients who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable. In TA429, the Committee agreed that the treatment effect in patients with a 17p deletion in the RESONATE trial who had previously had treatment (33% of patients) could be generalised to patients who had not had treatment.[7] Furthermore, in TA689, the Committee concluded that it was plausible to assume clinical equivalence between acalabrutinib and ibrutinib in previously untreated ‘high-risk’ patients based on data in the R/R setting and this was acceptable for decision making.

In this submission, following the precedent set by TA689 and TA429, MAICs conducted using ELEVATE-RR and ASCEND were generalised to the first-line 'high-risk' setting and used as a proxy to support reimbursement decisions in this population.[7,34] In ALPINE, the clinical benefits of zanubrutinib were observed across all pre-specified subgroups, including in patients with a 17p deletion or TP53 mutation. When assessing outcomes in patients with 17p deletion or TP53 mutations specifically, zanubrutinib was associated with a [redacted] % reduction in the risk of INV-assessed disease progression or death (HR:[redacted], 95% CI: [redacted]) and statistically significant [redacted] % reduction in the risk of IRC-assessed disease progression or death versus ibrutinib (HR:[redacted], 95% CI: [redacted]), which was at least comparable with the treatment effect observed in the ITT population where zanubrutinib is associated with a statistically significant [redacted] reduction in the risk of INV-assessed disease progression or death versus ibrutinib (HR:[redacted], 95% CI: [redacted]) and statistically significant [redacted] reduction in the risk of IRC-assessed disease progression or death (HR:[redacted]; 95% CI: [redacted]).

As discussed in the Company submission, the paucity of data specifically collected in previously untreated 'high-risk' patients renders an ITC specifically in this population unfeasible and proxy data from the R/R CLL setting is deemed appropriate for decision making, especially when combined with data for previously untreated patients irrespective of 'high-risk' mutation status. To supplement the comparison with ibrutinib, a naïve comparison (using data from Mato et al.[27]) was conducted to assess the efficacy of zanubrutinib with ibrutinib in patients with previously untreated CLL and a MAIC was conducted comparing zanubrutinib (using the pooled zanubrutinib data from SEQUOIA Cohort 1 and Cohort 2) with acalabrutinib in previously untreated patients with CLL who are unsuitable for FCR and BR therapy, both with and without 17p deletion. Both the MAIC and naïve comparison in previously untreated CLL supported the conclusions of non-inferiority demonstrated by the MAICs conducted in the R/R setting, confirming that it is clinically plausible to conclude that zanubrutinib is at least non-inferior to acalabrutinib and ibrutinib in all previously untreated patients including 'high-risk' patients.

B12. Section B.3a.3.4.2 (p. 191): "Cost-utility analyses are also explored in which the PFS HR generated in the MAICs and the naïve comparison versus Mato et al. (2018)

are applied to the TTP endpoint." How were these PFS parameters adjusted to estimate TTP and PrePS for the comparators in the model?

The PFS hazard ratio was not adjusted when applied to TTP and PrePS in the model. Since TTP and PrePS are components of PFS, it was assumed that the PFS hazard ratio could be used directly applied to these endpoints, with no adjustments made. It was not possible to generate the TTP and PrePS hazard ratios for use in the model since data on these endpoints has not been published from comparator trials and hence no ITC could be conducted. Furthermore, this approach was accepted during the appraisal for acalabrutinib for previously untreated and R/R patients with CLL (TA689).[7]

B13. Priority question. Section B.3b.2 (p. 224): Please provide further justification why a partitioned survival model (PSM) was considered appropriate for the R/R CLL population? The company state that PSM "require relatively mature long-term OS data" however as highlighted in this letter (A14) the SEQUOIA trial had longer-term OS data available.

As noted in the Company's response to Clarification Question A14, the relevance of OS data to inform the model was determined by the number of events rather than follow-up. As more deaths occurred in ALPINE, extrapolations of the OS data were considered more reliable despite the shorter follow-up and sufficiently robust to inform a PSM structure. In comparison, there were too few deaths in SEQUOIA to reliably extrapolate OS data, with the modelling likely to predict a large number of patients remaining alive at the end of the modelled time horizon.

The use of the semi-Markov model structure to model previously untreated CLL was also driven by a need for more detailed subsequent treatment modelling. In the UK, a BCL2i regimen is typically prescribed following progression on a front-line BTKi, with venetoclax-rituximab being considered the regimen of choice.[11] As the model assumes all patients would move to venetoclax-rituximab following progression on a BTKi, published data from MURANO was extrapolated and used to inform PPS in the model. This approach reflects the treatment pathway more accurately, is consistent with the approach used in previous NICE appraisals for previously untreated CLL and was supported by clinical experts and health economists at an advisory board conducted by the Company (03 November 2022).[7]

The PSM model was considered appropriate for the R/R CLL population as the structure is a widely accepted approach that has been used in previous NICE HTAs in R/R CLL (TA429, TA689).[7,34] Moreover, unlike in the treatment naïve population, it is not necessary to model multiple lines of subsequent therapy given the limited treatment options for patients in the R/R setting. Clinical experts and health economists in attendance at an advisory board (03 November 2022) held by the Company deemed the PSM structure suitable for the decision problem in R/R CLL.[11]

B14. Section B.3b.2.1, Table 100 (p. 227): What is the justification for the same body surface area value being used for the R/R CLL economic model (1.92m) as the treatment naive economic model when the age and weight characteristics are different in both of the economic models?

Body surface area (BSA) is calculated using the formula in Equation 1 below:

Equation 1: BSA formula

$$BSA\ (m^2) = \sqrt{\frac{weight\ (kg) * height\ (cm)}{3{,}600}}$$

cm – centimetres; kg – kilogram

In SEQUOIA, the mean weight of patients was 78.12 kg, and the mean height of patients was 169.65 cm. Inputting these values into Equation 1 results in a BSA of 1.9186 m^2. In ALPINE, the mean weight of patients was 78.53 kg, and the mean height of patients was 169.68 cm. Inputting these values into Equation 1 results in a BSA of 1.9238 m^2.

Rounding the calculated BSA values from SEQUOIA and ALPINE to two decimal places results in BSA of 1.92 m^2 for both economic models.

B15. Section B.3b.3.5.1 (p. 236): The company state that “the similarity between the unadjusted and adjusted PFS and OS KMs for zanubrutinib and acalabrutinib supported the non-inferiority of zanubrutinib to acalabrutinib.” What were the Kaplan-Meiers (KMs) adjusted for?

Based on the covariates listed in Sections B.2.9.2.1 and B.2.9.3.1 of the Company submission, individual patient data (IPD) from ALPINE was adjusted using balancing weights to match the baseline cohort characteristics of the ELEVATE-RR and

ASCEND trials, following the MAIC methodology. PFS and OS data from the adjusted ALPINE IPD (adjusted to match ELEVATE-RR and ASCEND within the respective MAICs) was then used to generate KM plots which were compared to the KM plots generated from the unadjusted ALPINE dataset.

B16. Appendix M, Table 1 (p. 1): Please clarify how zanubrutinib was stratified.

Zanubrutinib was stratified by separately fitting the six parametric curve distributions, as per NICE Decision Support Unit Technical Specification Document (DSU TSD) 14, to the individual patient-level data.[36] As such, stratified refers to the independent fitting of parametric curves (as opposed to dependent or joint fitting of curves).

Measurement and valuation of health effects

B17. Priority question. Section B.2a.6.3, Table 24 (p. 68): Table 24 summarises the mean change in EORTC QLQ-C30 scale scores from baseline at week 12 and week 24. Please provide the mean EORTC QLQ-C30 scale scores for each timepoint (i.e. baseline, week 12 and week 24) for each of the randomised arms.

The mean EORTC QLQ-C30 scale scores in Cohort 1 at baseline, Week 12 and Week 24 are presented in Table 10 below. At Week 24, treatment with zanubrutinib was associated with better overall outcomes across all patient-reported outcome (PRO) endpoints.

Table 10: Mean EORTC QLQ-C30 scores in Cohort 1 in SEQUOIA

PRO endpoint	Zanubrutinib			BR		
	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
GHS/QoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/ Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BR – Bendamustine-rituximab; GHS – Global health status; PRO – Patient reported outcome; QoL – Quality-of-life; SD – Standard deviation.
Source: SEQUOIA CSR[16]

B18. Priority question. Section B.2a.6.3, Table 24 (p. 68): Please provide the mean overall EORTC QLQ-C30 scores at each timepoint, including any data points available beyond week 24.

As per the EORTC QLQ-C30 Scoring Manual, the use of a total, global score based upon the sum of all items is strongly cautioned against and the Global Health Status (GSH)/QoL scale should be used as the overall summary measure.[37] Mean GHS/QoL scores from baseline to Week 24 are presented in Table 10 above and scores for timepoints beyond Week 24 are presented in Table 11.

Table 11: Mean GHS/QoL EORTC QLQ-C30 scores in SEQUOIA

GHS/QoL	Zanubrutinib (N=241)	BR (N=238)
Week 36	[redacted]	[redacted]
Week 48	[redacted]	[redacted]
Week 60	[redacted]	[redacted]
Week 72	[redacted]	[redacted]
Week 84	[redacted]	[redacted]
Week 96	[redacted]	[redacted]
Week 120	[redacted]	[redacted]
Week 144	[redacted]	[redacted]

BR – Bendamustine-rituximab; GHS – Global Health Status; PRO – Patient reported outcome; QoL – Quality of life.

B19. Priority question. Section B.3a.4.2, Figure 53 (p. 192): Please provide descriptive summaries (mean and measure of variance) of the EQ-5D-5L utility data for each time point for which data are reported in Figure 53.

Table 12 below provides descriptive summaries of the EQ-5D-5L utility data for each timepoint reported in Figure 53 of the Company submission.

Table 12: Descriptive summaries of EQ-5D-5L data in SEQUOIA

Assessment	Zanubrutinib (N=225)		BR (N=195)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 1	[redacted]	[redacted]	[redacted]	[redacted]

RA - WEEK 12	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 24	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 36	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 48	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 60	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 72	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 84	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 96	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 120	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 144	[redacted]	[redacted]	[redacted]	[redacted]

BR - Bendamustine-rituximab; CI - Confidence interval; RA – Response assessment; SD – Standard deviation.

B20. Priority question. Section B.3b.4.2, Table 42 (p.97): Table 42 summarises mean change in EORTC QLQ-C30 scale scores from baseline at cycle 7 and cycle 13. Please provide the mean EORTC QLQ-C30 scale scores at each timepoint (i.e. baseline, cycle 7, and cycle 13) for each of the randomised arms.

The mean EORTC QLQ-C30 scale scores at baseline, cycle 7 and cycle 13 are presented in Table 13 below.

Table 13: Mean EORTC QLQ-C30 scores in ALPINE

PRO endpoint	Zanubrutinib			Ibrutinib		
	Baseline	Cycle 7*	Cycle 13*	Baseline	Cycle 7*	Cycle 13*
GHS/QoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GHS – Global health Status; PRO – Patient reported outcomes; SD – Standard deviation; QoL – Quality-of-life
*One cycle = 28 days
Note: Only patients with data at both baseline and the each postbaseline visit were included in the summary statistics for change from baseline.
Source: ALPINE CSR[22]

B21. Priority question. Section B.3b.4.2, Table 42 (p. 97): Please provide the mean overall EORTC QLQ-C30 scores at each timepoint (i.e. baseline, cycle 7, and cycle 13).

As per the EORTC QLQ-C30 Scoring Manual, the use of a total, global score based upon the sum of all items is strongly cautioned against and the GSH/QoL scale should be used as the overall summary measure.[37] Mean GHS/QoL scores from baseline to Week 24 are presented in Table 13 above and scores for timepoints beyond Cycle 13 are presented in Table 14.2.1.12 in the ALPINE CSR.[22]

B22. Priority question. Section B.3b.4.2, Figure 61 (p.239): Please provide descriptive summaries (mean and measure of variance) of the EQ-5D-5L utility data for each time point for which data are reported in Figure 61.

Table 14 below provides descriptive summaries of the EQ-5D-5L utility data for each time point reported in Figure 61 of the Company submission, which was generated using data from the 31 December 2020 data cut-off. Since the Company submission, EQ-5D-5L data from the 01 December 2021 data cut-off has been analysed, with results presented in Table 15 and Figure 1 below.

Table 14: Descriptive summaries of EQ-5D-5L for ALPINE (DCO 31 December 2020)

Assessment	Zanubrutinib (N=280)		Ibrutinib (N=271)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; DCO – Data cut-off; NE – Not evaluated; SD – Standard deviation.

Table 15: Descriptive summaries of EQ-5D-5L for ALPINE (DCO 01 December 2021)

Assessment	Zanubrutinib (N=309)		Ibrutinib (N=300)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 31 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 34 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 37 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]

Assessment	Zanubrutinib (N=309)		Ibrutinib (N=300)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Long-term follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 8	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 10	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; DCO – Data cut-off; NE – Not evaluated; SD – Standard Deviation

Figure 1: Trial generated EQ-5D per treatment and visit – ALPINE (DCO 01 December 2021)

DCO – Data cut-off; LTFU – Long-term follow-up

B23. Section B.2a.4.2, Table 15 (p. 52) and Section B.2b.4.2, Table 33 (p. 82): Please provide justification that missing EORTC QLQ-C30 data were missing at random. Please also provide further details on how these data were analysed using mixed model repeated measures.

EOTRC data was analysed using a MMRM analysis which assumes that missing data is missing at random as a built-in feature of the model. Handling of missing data were in accordance with each PRO instrument's manual as described within the respective SEQUOIA and ALPINE SAPs (Section 5.2.3 for both).[37,38]

In addition, both completion rates and compliance rates (ratio of patients who completed the questionnaires to patients still in the treatment) were collected to account for reliability of the results due to missing data. The key clinical endpoints were selected ensuring that there were enough patients in both arms to obtain meaningful results. The number of patients and reasons for patients' dropouts in both arms were collected and reported in the SEQUOIA and ALPINE CSRs.[16,22] The

number of patients remaining on treatment and reasons for dropouts in each arm were taken into consideration when interpreting the PRO results.

Cost and healthcare resource use

B24. Section B.3a.5.3 (p. 202) and Section B.3b.5.3 (p. 245): Why does the inclusion criteria of Grade ≥ 3 adverse events change by population (1% for treatment-naïve CLL and 2% for R/R CLL)?

For both the previously untreated CLL and the R/R CLL populations, the inclusion criteria of Grade ≥3 AEs in the models were selected such that they would appropriately capture AEs that would impact patients in a real-world setting in which AEs are monitored in a less strict manner compared with a clinical trial setting.

In the R/R CLL model, a more stringent inclusion criteria of Grade ≥3 AE occurring in 2% of patients was selected. Patients with R/R CLL are more likely to suffer from AEs due to having experienced multiple progressions or being refractory to treatment. As AEs are more likely to occur in patients with R/R compared to the previously untreated population, a more stringent inclusion criteria relative to the previously untreated population ensures that only AEs which are beyond a reasonable uncertainty are incorporated in the model.[16,22]

It should also be noted that changing the inclusion criteria of Grade ≥3 AEs from 2% to 1% for the R/R population would only result in additional AEs being incorporated which occurred in few patients. Given that the one-way sensitivity analysis showed that the cost of AEs per cycle is not a driver of the results of the model, as presented in Section B.3b.11.2, this would have a minimal impact on the cost difference of treatment with zanubrutinib in patients with R/R CLL compared to treatment with ibrutinib or acalabrutinib.

B25. Priority question. Section B.3a.5 (p. 199) and Section B.3b.5 (p 242): What price year was used for costs?

All costs within the economic models were sourced from or inflated to the most recent 2020/2021 price year.

B26. Section B.3a.5.4.1 (p. 203) and Section B.3b.5.4.1 (p. 246): Data from Round, Jones and Morris (2015) was used to estimate terminal care costs. Were these costs inflated to a common price year and, if yes, what method did the company use?

The Round, Jones and Morris (2015) publication reported terminal care costs as £4,254 and £1,829 for health and social care, respectively. These costs were added together (£6,083) and inflated from a 2013/2014 to a 2020/2021 price year using inflation factors derived from EUROSTAT.[39] The Eurostat inflation indices are presented in Table 16.

Table 16: EUROSTAT inflation indices

Time	cp06 Health	Factor to 2021
2005	75.7	1.4914
2006	77.7	1.4530
2007	80.4	1.4042
2008	82.8	1.3635
2009	85.1	1.3267
2010	87.6	1.2888
2011	90.5	1.2475
2012	93.2	1.2114
2013	95.5	1.1822
2014	98.1	1.1509
2015	100	1.1290
2016	102.1	1.1058
2017	104.80	1.0773
2018	107.40	1.0512
2019	110.10	1.0254
2020	112.50	1.0036
2021	112.90	1.0000

Section C: Textual clarification and additional points

C1. On p.40 and 42 the abbreviation IRC is used for independent central review but from p.53 onwards the abbreviation refers to the independent review committee. Please confirm which of these abbreviations is correct and whether they refer to the same review.

The Independent Review Committee can be abbreviated to IRC. Referring to the Independent Central Review on page 40 and 42 was a typographical error.

C2. Please provide a list of abbreviations for the company submission, as there appear to be some inconsistencies in how abbreviations are used throughout Document B and there were some abbreviations missing from table footnotes.

A list of abbreviations used in the Company submission are presented in Table 17 below.

Table 17: List of abbreviations

AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike's Information Criterion
BCL2I	B-cell lymphoma 2 inhibitor
BCR	B-cell antigen receptor
BIA	Budget impact analysis
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine-rituximab
BSA	Body surface area
BSH	British Society for Haematology
BTKi	Bruton tyrosine kinase inhibitor
CC	Complication and comorbidity
CDF	Cancer Drugs Fund
CE	Cost-effective
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIT	Chemoimmunotherapy
CIRS	Cumulative Illness Rating Scale
CLL	Chronic lymphocytic leukaemia
CLL-IPI	Chronic lymphocytic leukaemia international prognostic index
CMA	Cost-minimisation analysis
CNS	Central nervous system
CR	Complete response
CT	Computerised tomography
CVD	Cardiovascular disease
DCO	Data cut off
Del11q/13q	Deletion of the short arm of chromosome 11/13
Del17p	Deletion of the short arm chromosome 17
DMC	Data monitoring committee
DOR	Duration of response
DP	Disease progression
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EMA	European Medicines Association
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group

ESMO	European Society for Medical Oncology
ESS	Effective sample size
EQ-5D	EuroQol Five Dimensions
FACIT	Functional Assessment of Cancer Therapy
FCR	Fludarabine, cyclophosphamide and rituximab-based
GHS	Global health status
GI	Gastrointestinal
HMDS	Haematological Malignancy Diagnostic Service
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IGVH	Immunoglobin heavy chain gene
IR	Idelalisib-rituximab
INV	Investigator
IPD	Individual patient-level data
IPI	International prognostic index
IR	Idelalisib-rituximab
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
Kg	Kilogram
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDi	Longest diameter
LS	Least squares
LY	Life year
LYG	Life years gained
m	Metre
MAIC	Matching-adjusted indirect comparison
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model repeated measures
NA	Not applicable
NHL	Non-Hodgkin's Lymphoma
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PC	Physician's choice
PD	Progressed disease
PF	Progression-free

PFS	Progression-free survival
PH	Proportional hazards
PPS	Post-progression
PR	Partial response
PrePS	Pre-progression survival
PRL	Partial response with lymphocytosis
PRO	Patient reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival models
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality-of-life
RCT	Randomised control trial
RIPD	Reconstructed individual patient data
RR	Relapsed or refractory
SAE	Serious adverse event
SE	Standard error
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SmPC	Summary of product characteristics
STC	Simulated treatment comparison
SYK	Spleen tyrosine kinase
TA	Technology appraisal
TEAE	Treatment-emergent adverse events
TLS	Tumour lysis syndrome
TN	Treatment naïve
TP53	Tumour protein P53 gene
TTP	Time-to-progression
TTD	Time-to-discontinuation
TTTF	Time-to-treatment failure
UK	United Kingdom
VAS	Visual analogue scale
VR	Venetoclax-Rituximab
WM	Waldenstrom's macroglobulinaemia
1LTx	First-line treatment
2LTx	Second-line treatment

C3. Section B.3a.11.2, Figure 55 and Figure 56 (p.213) and Section B.3.b.11.2, Figure 63 and Figure 64 (p. 255): Please update the Tornado diagrams to include the upper and lower values.

Figures 55 and 56 from Section 3a.11.2 and Figures 63 and 64 from Section B3b.11.2 have been updated to include the upper and lower bound values. The updated Tornado diagrams are provided below.

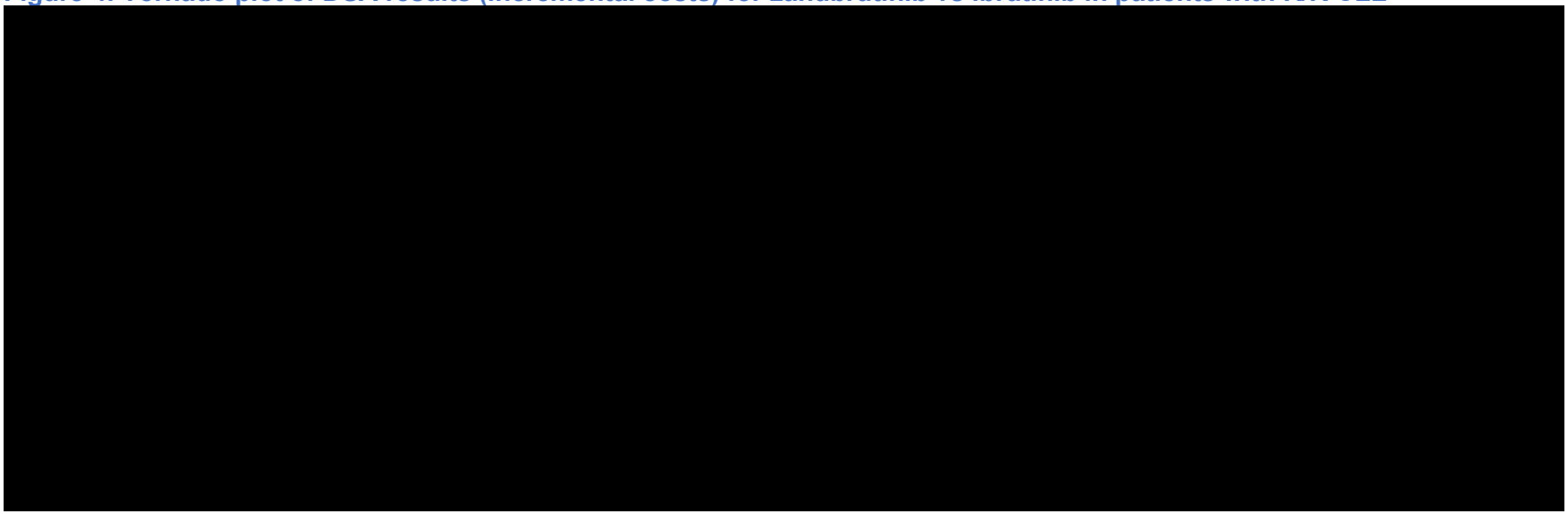
Figure 2: Tornado plot of DSA results (incremental costs) for zanubrutinib vs ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; TPP – Time-to-progression.

Figure 3: Tornado plot of DSA results (incremental costs) for zanubrutinib vs acalabrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; TPP – Time-to-progression.

Figure 4: Tornado plot of DSA results (incremental costs) for zanubrutinib vs ibrutinib in patients with R/R CLL



AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or refractory.

Figure 5: Tornado plot of DSA results (incremental costs) for zanubrutinib vs acalabrutinib in patients with R/R CLL

AE – Adverse event; CLL – Chronic lymphocytic leukaemia; DSA – Deterministic sensitivity analysis; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or refractory

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	CLL Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**CLL Support** is the only UK CLL specific support charity which was formed in 2005 and is run entirely by volunteers. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLL Support provides support to the UK CLL community and CLLSA membership of 2,000+ association members who live with CLL or are carers and the 20,000+ CLLSA on-line community members on the Health Unlocked CLL Support platform (not all UK based). CLL Support provides up to 6 patient conferences a year including a regular Scottish patient's conference. Since 2020 the majority of the meetings have been via Webinars because of COVID19 although face to face meetings have recently resumed. CLL Support supports patients through telephone, email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and their online presence on Health Unlocked https://healthunlocked.com/cllsupport. The CLL Support website, https://www.cllsupport.org.uk , also focusses on the mental wellbeing of CLL patients. The association is supported and generously funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from various pharmaceutical companies.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Most recent funding information AstraZeneca – £15,000 Core funding of member services Abbvie - £12,000 Core funding of member services Roche – £16,000 Core funding of member services Janssen - £7,500 Core funding of member services Beigene - NONE
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information contained in this report has been collected from pre-existing case studies and direct quotes from patients in contact with our support team and has also been informed by an analysis of the experiences and views of patients, family members and carers gathered via our online platform on Health Unlocked and a survey created in Q4 2022 by CLL Canada Care, which was disseminated via our patient communities. We acknowledge that the survey had limited responses from CLL patients who had been treated with Zanubrutinib and that the respondents were self-selecting and so likely to be biased towards our existing patient network's groups who tend to be proactive and informed groups of patients. However, the Health Unlocked community had approximately 30+ members who shared their experiences anonymously.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL is a complex disease. It takes an average of around 3 months from onset of symptoms (if the patient has any) to diagnosis odten requiring repeated visits to healthcare professionals. This has a significant emotional impact as people affected know something is wrong. This impact continues throughout the treatment pathway for both patient and carers particularly during the 'watch and wait phase'. In our older and recent surveys, the common issues reported at diagnosis include fatigue (51.6%), increased lymphocyte count (48%), enlarged lymph nodes (39.1%), frequent infections (21%), night sweats (19.4%), enlarged spleen or discomfort on upper left side of stomach (15.7%), shortness of breath (15.3%), anaemia (13.7%), thrombocytopenia (10.5%), pain (8.1%), fever (5.6%) and neutropenia (5.2%). In around 7 in 10 cases, CLL is discovered by chance during investigations for something else. This can be psychologically challenging for patients when they are given their diagnosis, especially if their plan is watch and wait. Patients told us: • *"I was told I had leukaemia and hardly heard anything else that the doctor said after that except that I wasn't having any treatment! I was so scared."* • *"We felt so worried, knowing that I was having to wait to get worse and worse before they would treat me. I thought I would probably die first."* • *"I already felt so tired and ill and it had taken ages to get a blood test but I was told I wasn't ill enough for treatment. I was so upset"* • *"Sometimes I catch my wife staring at me and I know she's desperately worried I'm going to die"* Most people have not heard of CLL before their diagnosis. Once diagnosed, they are likely to focus on the 'leukaemia' aspect, as they understand this as a form of cancer. Often, there is not sufficient focus on the chronic, long-term nature of the disease and the watch and wait plan during the initial consultation. The most common approach to managing CLL is active monitoring, most commonly known as watch and wait. This is a challenge for people to understand and come to terms with. They have a cancer diagnosis but there is not any immediate treatment action. Family and friends are also confused and can even question the diagnosis as they feel that 'cancer' needs to be treated as soon as possible. CLL is a very heterogeneous disease and whilst approximately only one third of patients experience few symptoms at diagnosis, almost all will develop increasingly uncomfortable symptoms as their disease progresses. Two thirds will be monitored under "watch and wait" (active monitoring) until treatment becomes necessary because of an increasing and uncomfortable symptom burden. The other third will require treatment not long after or immediately after diagnosis. The negative emotional and psychological issues experienced at diagnosis remain high for the majority of patients during the watch and wait period: "stress" (75.8%), "anxiety" (59.3%), "difficulty sleeping" (38.7%) and "depression"

	(30.6%). These percentages were similar in both the recent and preceding survey and affect not just the patient but their carers and family. For almost all patients, CLL is incurable. Any treatment usually ends in eventual relapse so patients live in a cycle of 'waiting, monitoring, treatment, monitoring again then relapse', which is repeated and continues until death. Patients worry about relapse, knowing further toxic treatment is likely to impact negatively on their quality of life. Even after a period of successful treatment, patients can be left with a significant symptom burden and poor quality of life, uncertain as to what will happen next. It is psychologically challenging know that symptoms, quality of life and clinical assessments are likely to worsen, and then further treatment will be required which is likely to be less effective than the last. CLL tends to respond less well to each line of therapy, with shorter subsequent remissions. Around 85% of patients diagnosed are aged 65 or older and many also have comorbidities. This means the more toxic treatments are not well tolerated by the majority of patients which negatively impacts on treatment effectiveness and quality of life. This is especially difficult for younger patients who will inevitably face multiple lines of treatment. Some have to give up work because of fatigue and then struggle financially, physically and emotionally. As CLL is a genetically evolving disease which acquires mutations as time progresses and in response to treatment, many patients are also concerned that they could experience Richter's transformation to an acute form of lymphoma, which is a rapidly progressing and generally an 'end of life' event. Patients with CLL have an increased risk of infection, as their immune system is severely compromised by the disease even during the watch and wait phase. These frequent and persistent infections impact hugely on quality of life, as well as being a leading cause of death for CLL patients. During the winter, many patients, and their families, experience long periods of isolation to try to reduce the risk of infection. As outlined above, living with CLL is difficult and does not affect the patient alone, but creates a "ripple effect", impacting on the whole family and even friends and colleagues. Covid has increased the isolation and limited lifestyle of CLL patients and their families/carers. Family members/carers can be challenged with exhausting caretaking duties when someone they know is diagnosed with CLL. Carers cited having to take on previously shared household duties. Many had to give up their own jobs, adding to the negative financial impact that living with CLL can cause. Patients' compromised immune systems and treatment side effects were cited by 20% of as a reason for reduced social contact with family and friends for both caregivers and patients. Some have sacrificed holidays and non-essential social events because of it. This will have increased since covid and it has been widely reported that the majority of CLL patients, particularly those having active treatment, are unlikely to mount an antibody response to multiple vaccinations. In the survey 60% of patients reported their family, work, social life and travelling/holidays was curtailed by their CLL and trying to stay safe and free of infection. 27% said they felt 'isolated'.

	Patients report: • *"I had to retire because of fatigue and the financial impact has been huge. I don't get any disability benefits because the symptoms I have are not detectable on examination"* • *"I am very concerned about infections as my antibody levels are low and I cannot get immunoglobulin treatment as it seems to be more restricted."* • *"With Covid, flu and respiratory illnesses increasing around us, I'm trying to minimize my contact with others in larger social settings and I no longer go to the cinema etc"* • *"Fatigue does not allow me to do all things I want. I get tired easily and have to pace myself."* • *"I worry that I won't be able to do my job as it's very demanding. So that is always on my mind. How will I support myself and my family if I can no longer work."* Living with CLL is living with ongoing, stressful uncertainty for both the patient and carer – uncertainty about disease progression, length of life, quality of life, possible infections and an inability to live a 'normal' social life. The COVID19 pandemic has further restricted their opportunities for social and leisure activities.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	CLL is regarded as incurable and treatment goals and strategies need to be selected to suit individual needs. These will depend on the subtype of CLL that the patient has, the treatment history, overall health, fitness, co-morbidities risk, treatment goals and patient choice. Patient's main concerns are that a non toxic, effective treatment that is suitable for them, will not be available to them when they need it, either first treatment or for relapse. In our survey, all CLL patients wanted to transition from chemotherapy to an era of targeted therapy with proven efficacy. Every age group valued new treatments with fewer and more tolerable side effects. **For treatment naïve patients** For some treatment-naive patients, those with high risk 17p deletions and TP53 mutations, and for the less fit patients, the introduction of NICE approved targeted therapies has provided treatment options that have improved survival and quality of life without the toxicities associated with chemotherapy. However, not all the targeted treatments are suitable for all patients because of off target side effects which can also impact very negatively on quality of life and lead to cessation of treatment. Numerous patients reported that hypertension, AF, diarrhea and joint pains had led to them stopping Ibrutinib. Acalabrutinib was better tolerated with regard to joint pains and hypertension but incompatible with those that needed a PPI or suffered from migraines. One Ibrutinib patient explained "*I suffered horrible diarrhoea, great exacerbation of my hypertension, bone pain but finally after pneumonitis they pulled me off of it and boy was I glad. Ibrutunib did the job and quickly but boy the cost to me and the AE dept at my local hospital was high".* Fitter patients who do not have the high risk 17p deletions and TP53 aberrations, irrespective of IGHV mutation status, are still sometimes given more toxic chemo-immunotherapy regimens. However, patients with unmutated IGHV or complex genetics also do poorly with chemo-immunotherapy and do not have the automatic right to access a NICE approved targeted therapy (Acalabrutinib TA689 and Venetoclax + Obintuzumab TA 663 via the Cancer drugs Fund) if their doctor decides that chemo-immunotherapy is suitable for them. Chemo-immunotherapy treatment has a considerable impact on quality of life and may mean hospital admissions and cumulative toxicities over the patient's lifetime, including the risk of incomplete restoration of bone marrow function, future myelodysplasia and acute myeloid leukaemia. This is an unacceptable healthcare inequality for 'fit' patients without the 17p and TP53 d genetic abnormalities. **Relapsed and refractory patients** Because CLL almost always relapses after a variable period of time, CLL patients require repeated and different treatments. Following relapse, patients generally respond less well, with shorter remissions, to each subsequent line of therapy. In our survey the majority of patients had received between 1 and 4 lines of treatment. Targeted therapies are available for all patients with relapsed or refractory CLL but the safety profile of each drug must be carefully matched to the patient's clinical condition and their co-morbidities which are common in these

	patients who are generally older in age. For relapsed patients, the cardiac side effect of atrial fibrillation with Ibrutinib is a particular concern. They are aware of the reported adverse events of AF, hypertension, arthralgias, musculoskeletal pain, rashes and the small number of sudden cardiac deaths. These side effects can become intolerable for patients forcing them to dose reduce, pause or stop treatment, which has a significant impact on their response. Ibrutinib is contraindicated for some cardiac patients and those who need to take anticoagulants. It has been shown to induce hypertension, new or worsened, in 72% of patients, with a two-fold higher risk of other cardiovascular events such as heart failure, stroke and sudden cardiac death. Acalabrutinib has a better cardiac safety profile but hypertension, new or worsening, is also reported and severe headaches are a common side effect that leads to discontinuation. Reference: https://ashpublications.org/blood/article-abstract/134/22/1919/375010/Hypertension-and-incident-cardiovascular-events For many patients these side effects diminish over time but not all. This patient's experience is not unusual: "*My own experience of Ibrutinib is of crippling joint pain, unbearable muscle cramps and hypertension, all ongoing after almost 5 years of treatment."* *Another said "the diarrhea was awful and explosive, I always needed to be near a toilet. I couldn't go out much, I was anxious about it"* Acalabrutinib (TA689) has an improved toxicity profile compared to Ibruitnib but some patients cannot tolerated the headaches, joint pain and there are now some cardiac toxicity signals on longer follow up. Idelasilib has a toxicity profile that many doctors and patients find unacceptable. None of the patients in our survey had experience of this drug. Venetoclax (TA796) and Venetoclax plus Rituximab (TA561) often requires multiple attendances or overnight stays for several weeks in hospital as the dose is ramped up because of the high risk of tumour lysis syndrome. Delivery of the rituximab also requires an appointment in the day unit. This is an effective treatment but the cytopenias that can occur mean pauses, delays and dose reductions whilst blood counts recover so is not suitable for everyone. This patient's comment regarding Venetoclax was typical "*I was happy to have a time limited treatment but underestimated the intensity of the ramp up. I felt as though I lived at the hospital and got quite fed up with it all and the blood tests"* Patients who experience disease progression or relapse and who have discontinued a targeted treatment due to intolerance of side effects, have a dismal outlook because options are limited. For these Zanubrutnib may offer a potential option.

8. Is there an unmet need for patients with this condition?	Yes, there is an unmet clinical need that Zanubrutinib would address for both treatment naïve (TN) and relapsed/refractory (RR) patients. Zanubrutinib appears to offer excellent effectiveness and be a relatively non-toxic BTKi treatment that can produce durable remissions with less side effects than the currently available BTKi's irrespective of patient co-morbidities, CLL genetics and IGHV mutation status.That unmet need is especially urgent for untreated 'fitter' patients who do not have the automatic right to a NICE approved targeted treatment if they do not have a 17p del or TP53 mutation. Within this group, those with complex genetics and unmutated IGHV have the greatest unmet need as they do very poorly with chemo-immunotherapy. Although the SEQUOIA study recruited unfit patients it is reasonable to extrapolate that fit patients would have a response which would be at least non-inferior. We cannot overstate the importance and the need for a range of treatment options for patients with CLL given the heterogeneity of both the disease and patient population. Zanubrutinib would be a welcome and valuable addition for both treatment-naïve and relapsed/refractory patients fulfilling a huge unmet need. It could prove to be more cost effective long term due to more durable remissions and less side effects that need investigating and treating • *I'm very pleased with this therapy (Zanubrutinib), compared to Ibrutinib it has been a walk in the park* • *I've been on Zanubrutinib for four months now after having serious issues with Ibrutinib. The first month was rough with a lot of bruising and petechiae all over my body then the issues seemed to resolve itself.* • *I had previously been intolerant of ibrutinib and came off it. I went on Zanubrutinib and I've had none of the previous side effects, just easy bruising and my fatigue remains although less so than before.* Because of the heterogeneous nature of CLL and the wide age range of patients who will have variable levels of fitness and comorbidities, a wide range of treatment options is important.
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Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients will naturally prefer a treatment that has less side effects with greater effectiveness (perhaps due to better compliance). Patients are aware of Zanubrutinib from reports on social media and online CLL communities including the results of the head to head study of Ibrutinib v Zanubrutinib for relapsed patients with CLL or SLL (https://www.nejm.org/doi/10.1056/NEJMoa2211582) where progression-free survival was significantly longer and fewer cardiac adverse events were reported among patients who received Zanubrutinib (ALPINE Study). Early reports from both clinical trials and real-world surveys for both treatment-naïve and refractory patients indicate that Zanubrutinib offers a highly effective treatment which is superior to Ibrutinib and with a better safety profile which makes it suitable for almost all patients, including those with cardiac risk factors and those that need to take a proton pump inhibitor. Patients that are intolerant of either Ibrutinib or Acalabrutinib because of side effects have been reported to be tolerant of Zanubrutinib and able to continue treatment with a BTKi, leading to control of disease and remissions. Because Zanubrutinib causes less cardiac issues than Ibrutinib and they also appear to be less than with Acalabrutinb (from the limited reports) then Zanubrutinib should also be more cost effective as those long term side effects will arise and require treatment. A better tolerability profile should lead to better compliance and improved disease control and potentially, a delayed need for subsequent treatments. Overall this should provide a better quality of life for patients Reports from patients who have experience of Zanubrutinib are overwhelmingly positive. These reports are from the online Lymphoma Canada survey and the CLL HU community. The respondents were across a wide range of ages: 63% were age 35-64 years; 37% aged greater than 65 years, including 10% greater than 75 years. A small number of patients had switched from Ibrutinib or Acalabrutinib to Zanabrutinib because of intolerance and were able to tolerate Zanabrutinib well which led to better compliance and disease response. Of the limited number of respondents approx. 100% of patients reported either a good or excellent experience of Zanubrutinib and reported that their health and general wellbeing had improved. Most patients had accessed Zanubrutinib via a compassionate access scheme or in a clinical trial and patients were predominantly from UK, USA, Canada. 40% of patients reported no side effects at all, 40% reported bruising or petechia which may appear as a rash (which improved over time), the remaining 20% were an unspecified nature. There were no patient reports of hypertension, diarrhoea, nausea, joint pains or infections – all of which are more common with Ibrutinib and Acalabrutinib. Patients appreciate that the treatment is a tablet that is taken at home, albeit twice a day, reducing their need for hospital attendance. Less side effects mean that patients are much more likely to comply with the treatment and this should lead to improved response and longer remissions.

	Patient comments include: • *"I have been on Zanubrutinib since 2018, I feel great and I am doing very well with no side effects"* • *I was prescribed Zanubrutinib because Ibrutinib and Venetoclax were too toxic for me and I suffer from migraines so Acalabrutinib was out"* • *I've had a lot of bruising but little else* • *It's an easy treatment for me. I'm told that I'm doing well and should do for many years. I have some peace of mind now about my CLL.* • *I really appreciated not having to go to the hospital all the time, I go every 3 months and that's it.* • *I feel well again and back to the old me. I returned to work which has been great for lots of reasons."* • *I have been taking Zanubrutinib for 25 months, delivered fantastic results and the drug has been very kind to me* • *My elderly mom has been on Zanubrutinib for 15 months and it's literally been a life saver for her. Her Hb rose from 80 to 114 and she has had no side effects apart from a rash which disappeared as the doctor said it would.* • *My only adverse effect was lots of petechiae on my head and body which improved over time*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?
Twice a day dosage may be seen as a slight disadvantage. The ongoing nature of the treatment may be seen to be a disadvantage by some patients; however, others find it a comfort to continue treatment. Current studies (STATIC) may mean that BTKi treatment can be stopped or paused in patients with good remissions and then started again as necessary. 40% of patients reported a petechial rash and/or bruising. For some patients this was a worry and unsightly but if patients were alerted that this may happen early in treatment then patients may be less anxious about it. A small number of patients, 5%, had experienced minor bleeding in the form of small skin haematomas. Patients could be concerned over cardiac issues with Zanubrutinib. However, Zanubrutinib performed significantly better in terms of atrial fibrillation in the trials and there were no fatal cardiac events reported.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Because of the heterogeneous nature of CLL and the diverse population, with and without co-morbidities, who require an effective, non toxic, treatment, it is difficult to identify one population that would benefit more than others. However, treatment-naïve patients of all ages and fitness especially those with complex genetics and/or unmutated IGHV status are most likely to benefit more from this technology because they have a less favourable response to chemo-immunotherapy and targeted therapies are not automatically available to them outside a clinical trial.This health inequality needs to be addressed. **Please note that we would prefer this treatment to be available to <u>ALL CLL</u> patients receiving their first and any subsequent treatments.**

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are definitely equality issues if Zanubrutinib is only approved for 'unfit' and relapsed patients and the approval is not inclusive of all treatment naïve patient groups irrespective of genetics. This will particularly affect treatment-naïve patients who have complex genetics and/or an unmutated IGHV status and do not have access to targeted treatments that will give them remissions of equal depth and length that other TP53 and 17p del patients experience.

Other issues

13. Are there any other issues that you would like the committee to consider?	We are presently and for the immediate future, affected by COVID-19, which still presents a real danger to the lives of CLL patients, many of whom are not able to produce antibodies despite multiple vaccinations. In 2020 the UK CLL Forum posted a consensus document on their website. Their advice is the agreed view of a body of experts in CLL in current UK practice to mitigate the risks to CLL patients from COVID-19 . The advice presented is not part of routine practice but is hoping to mitigate against the risk of infection and hospitalisation in CLL patients. The document states, "*avoid Fludarabine and Bendamustine*," because of the risk of severe immunosuppression and risk of infection. For treatment-naïve patients needing to start treatment, "*consider Chlorambucil Obinutuzumab as alternative for all*." However, as patients we do not consider this an effective treatment and it could prejudice overall survival, progression free survival and response to future treatments. To have Zanubrutinib approved for ALL treatment naïve patients would mean a safe, effective and well tolerated treatment for CLL patients irrespective of genetics, IGHV mutation status and fitness status. https://ukcllforum.org/wp-content/uploads/2020/04/UKCLL_COVID19_practical_b.pdf

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	In up to 5 bullet points, please summarise the key messages of your submission: • Access to multiple treatment options is important for EVERY CLL patient. CLL patients need access many different lines of treatment options because of co-morbidities and for multiple relapses. • Zanubrutinib addresses an unmet need for ALL CLL patients but especially for those who are fit and treatment-naïve without 17p del or TP53 mutations (they may have complex genetics or an unmutated IGHV status). These patients do not have the automatic right to access effective, non chemo-immunotherapy treatments as do every other group of patients. • Zanubrutinib is an effective treatment that induces deep remissions, with apparently fewer off target side effects than either Ibrutinib or Acalabrutinib which leads to improved compliance and response rates. • Zanubrutinib can be suitable for patients with cardiovascular risk factors, those on anticoagulants, those who need to take a PPI and those who suffer with migraine headaches. • Zanubrutinib would offer an effective and relatively safe, non-toxic option for all CLL patients needing to start first or subsequent treatment, which is especially important during the current ongoing endemic COVID-19 .

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** is the UK's leading leukaemia charity, founded in 1969. We are dedicated toensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies,community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Abbvie: £12,000 core funding and £450 honorarium Astrazeneca: £15,000 patient support Gilead: £25,000 core funding and £420 honorarium Janssen: £10,000 support activities for patients and £180 honorarium Pfizer: £10,000 core funding

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information for this submission was gathered through a number of sources. Surveys consulted include Leukaemia Care's 2017 and 2021 'Living with Leukaemia' survey alongside a new survey (2023) conducted for the purpose of this submission, which generated 271 responses from CLL patients. Of these 271 respondents, 4 patients had previously taken zanubrutinib. Many of the quotes in this submission come from this survey. Additional quotes were gathered through other one-to-one patient discussions, analysing patient stories, support groups and from patient panel meetings.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	*Patient experience* Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia. The risk of developing CLL increases with age, it is most common in older adults, with a median age at diagnosis of between 67 and 72 years. Taking into consideration the physical, emotional, and financial impact on CLL patients as well as the impact on their carers, a CLL diagnosis greatly affects a patient's quality of life. In a 2022 survey patients told us: *"Being told was a bad experience. As soon as I heard the word leukaemia …My grandmother had leukemia and she went into hospital and never came out again. I thought the world had stopped"* *"The prognosis was on the screen when he told me. I thought I was going to be dead and buried"* *"It was a huge shock at diagnosis! Incredibly scary. There were no support groups. I eventually learned to put it back in its box between appointments."* From diagnosis, CLL has a negative impact on an individual's mental health. The 2017 'Living with Leukaemia' Survey from Leukaemia Care reported 38% of CLL patients felt more anxious or depressed since diagnosis. Patients can sometimes feel they are a burden to carers which also has a knock-on effect for both their physical and mental health. One CLL patient commented "*After being discharged from hospital I decided not to worry my family and kept things bottled up. Looking back now that was the wrong decision."* CLL patients are especially prone to relapsing-remitting and, as CLL is incurable, patients will often be thinking about their next treatment and worrying about what challenges this might bring, including whether it will work in bringing about a response. A CLL patient we spoke to who has had multiple lines of treatment said, *"To live with CLL, every day you know you cannot be cured of this cancer"*. The ongoing stress and mental health impact of CLL treatment on the patient as well as their family, friends and carers can therefore also be significant. Living with untreated CLL often also has physical side-effects for patients, such as fatigue, fever, night sweats, weight loss, weakness etc. Furthermore, CLL patients who receive active treatment, such as intensive chemotherapy, will experience a range of additional side-effects, which can negatively affect patients physically in both the short-term and the long-term.

	It is also necessary to note the financial impact living with CLL has on the patient, due to time taken off work, reducing work hours or retiring and increased costs of travel to appointments, parking costs etc. One CLL patient said *"So, for my colleagues at work, knowing the news of my chronic condition, it was business as usual after a while. I tried to make it for myself too. Of course, my body wouldn't have it and the fatigue got worse over time, so I eventually resigned".* Those with CLL have an increased risk of infections due to their immune systems being compromised. Infection risk can be worsened by treatment too *"During my treatment I suffered from many infections which results in admission to hospital. So, after my treatment I was very weak and could not walk very far and was always tired*". Infections are the second highest cause of death related to CLL after disease progression (Strati P, Parikh SA, Chaffee KG, et al., 2017). This means patients have to take extra precautions, affecting their lives, to protect themselves, which undoubtedly has a negative effect on patients who are not able to engage with society as usual and can feel isolated. *Carers' experience* One CLL patient describes the psychological impact her CLL diagnosis had on her husband, saying "*he kept things to himself, he wouldn't speak to anyone".* Other CLL patients have told us that it can sometimes be harder for the person supporting the patient than for the patient themselves, as they need support in different ways, and this is often not readily available.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	In our most recent survey (2023) 81% of CLL patients thought that existing CLL treatments were not sufficient, or they were unsure. We then narrowed this down further by asking whether respondents thought there were enough CLL treatment options specifically for people who have already tried one or more treatments (i.e., relapsed/refractory), and 94% said no or not sure.
8. Is there an unmet need for patients with this condition?	There are currently significant unmet needs for CLL patients with regards to the treatment options available. In our most recent survey (2023), we asked patients whether there is anything they feel is not being addressed by the treatment options currently on offer. One patient who is currently untreated commented "*Undoubtedly if and when that time comes will research available treatments. I would want to be active in what is offered, and any decision making*". This highlights the patient's desire to have the option to choose the most appropriate treatment for them with their clinician, which is only possible if there are a number of options to choose from in the first line setting. Furthermore, another patient who is further along their treatment pathway also emphasized the need for more options by saying *"I've had several treatments during my 28 years. The next option may be the last option currently. Tablets are a much more convenient option, but the next treatment involves trips to hospitals for infusions. We had to abandon my last treatment, not because it wasn't working, but because of side effects*." Patients also describe the worry of running out of treatment options: *"It's good to have more non chemo options now for relapsed but it does feel like each treatment is just kicking the can down the road then hope there will be something else available when the time comes. Survival is my main concern".* Another patient commented *"I'm currently on Acalabrutinib seems to be working well for now but I'm always concerned about what will happen if that fails, what come next? Is there further drugs/treatments. It's always in the back of my mind."* In our survey, we asked whether patients ever worry about running out of treatment options, the majority (64.6%) said yes and a further 20.1% were not sure. There is therefore an unmet need for additional treatments at both the untreated and relapsed/refractory stage of the pathway to prolong the point at which a patient has run out of treatments when their only alternative is best supportive care.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	For all cohorts being considered for this treatment (fit patients in first-line, unfit patients in first line and relapsed/refractory patients), zanubrutinib would provide a much-needed alternative treatment option that would address many of the unmet needs outlined above. Clinicians and patients prefer to have greater options when it comes to the treatment of CLL, especially as these patients are prone to relapse/remitting and this allows doctors to create more personalised and tailored treatment plans. Patients who are in the fit untreated category would find zanubrutinib valuable as an additional treatment option, as there are currently fewer alternatives for this cohort. Majority of the existing treatments in this group, FCR and BR, are known to have more severe side effects, which can significantly negatively impact a patient's quality of life. Zanubrutinib's side effect profile seems to be favourable against the comparators in both the trials and in the experience of patients from our survey. 100% of UK patients in our 2023 survey who had taken zanubrutinib (4 respondents) said treatment with zanubrutinib managed all of their CLL symptoms. One patient commented on their positive experience with zanubrutinib by saying *"I have been taking zanubrutinib for over three years - my symptoms (extremely swollen lymph nodes were the 'obvious' one) were quickly brought under control and I have had no recurrence. The side effects I think have been minimal - bruising easily being the most long lasting. Having had FCR in 2013 I can definitely say that the treatment with zanubrutinib is infinitely better!".* These patient perspectives were supported by trial outcomes. For the unfit patients in first line a study showed that zanubrutinib appears to have fewer side effects than BR (bendamustine, rituximab). Furthermore, a reduction in cardiac events with zanubrutinib in comparison to ibrutinib in the trial means that zanubrutinib could be an additional option for patients with cardiac comorbidities in first line or in the relapsed/refractory setting. These people have fewer options due to the link with ibrutinib and cardiac events. One CLL patient described the importance of this by saying *"as a CLL patient with a history of cardiac related challenges, it is important to me that I don't run out of options of suitable maintenance treatments which enable the management of my CLL and offer me a good quality of life."*

	In the relapsed/refractory setting, zanubrutinib would also help to alleviate the aforementioned worry and anxiety that patients experience when they have had several lines of treatment and worry about running out of options. Additionally, the ALPINE study showed that progression free survival (PFS) is superior with zanubrutinib in head-to-head comparison with ibrutinib in relapsed/refractory setting, including in people with high-risk genetics. There was also a phase 2 study showing that zanubrutinib was tolerated by people who had already had acalabrutinib and ibrutinib. So, if people who had taken acalabrutinib or ibrutinib previously had stopped due to side effects/intolerance, then zanubrutinib would provide another option for them. Finally, our 2017 Living with Leukaemia survey shows CLL patients (59%) favour zanubrutinib's method of delivery, oral tablet, over all other treatment methods of delivery. There are other oral therapies in the treatment of CLL already, but not all are available to all patients, for example there are currently no oral treatments available in first line for CLL. Furthermore, patients who have run out of other treatment options would favour additional options being oral treatments. The reasons for this preference can often be attributed largely to convenience. Oral treatments take less time, are less invasive and can often be taken at home requiring reduced travel to and time in hospital. This can have positive financial implications on patients, as well as giving them more time to live their day-to-day lives.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The head-to-head trial with ibrutinib showed that a side effect of zanubrutnib, neutropenia, affected slightly more people at a slightly higher grade than with ibrutinib. Neutropenia causes patients to have an increased risk of infection, however CLL patients are often used to this and aware of how to reduce their risk of infections. Furthermore, when you look at the actual infections that were reported with zanubrutinib, these were lower compared with ibrutinib. Another adverse event for zanubrutinib was also hypertension (high blood pressure), which performed similarly to ibrutinib in the trial. Ibrutinib has also been linked with adverse cardiac events so there could therefore be a similar concern over cardiac issues with zanubrutinib. However, zanubrutinib performed significantly better in terms of atrial fibrillation and flutter than zanubrutinib. Furthermore, there were no fatal cardiac events seen zanubrutinib, and less adverse events overall that lead to dose reduction in comparison to ibrutinib.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We are concerned that the untreated fit population may not be adequately considered. The only treatment options available in this cohort are FCR and BR, but these are typically not favoured by clinicians due to their side effects and association with adverse events. Venetoclax obinutuzumab has been available on the CDF in recent times, but we are concerned that access to this could be prohibited after the CDF. Furthermore, even if venetoclax obinutuzumab remains an option, there is still a strong unmet need for otherwise fit patients to have access to treatments with fewer significant side effects, more convenient modes of delivery (e.g., oral tablets), and greater choice for clinicians and patients alike. Patients in the untreated unfit population would also benefit because zanubrutinib would give them another single therapy option in first line with improved side effects and PFS chances. Clinicians can feel the need to use combination therapies in first line in order to provide a tailored/personalised treatment plan that suits the individual patient, but this results in there being fewer options in the relapsed/refractory setting. Therefore, adding more single targeted therapies in the first line allows for greater choice for both clinicians and patients, and might lengthen the time before a patient runs out of treatment options. Patients in the relapsed/refractory setting would also benefit from the approval of zanubrutinib, as trial studies have shown it is superior to comparator ibrutinib in terms of PFS in this setting. Additionally, when patients have tried several of the existing treatments in the past, the worry about what's next and whether they will run out of options affects the quality of life of patients. Therefore, adding additional treatment options, such as zanubrutinib, in this setting would not only improve PFS but also improve patients' quality of life for this reason. For example, it could further extend the life of a CLL patient, allowing them to spend more time with friends and family. We therefore believe there is an unmet need in all of the subgroups being considered in the scope, and urge NICE to ensure Zanubrutinib is available for all groups, as this is a treatment which addresses unmet needs in every cohort.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/a

Other issues

13. Are there any other issues that you would like the committee to consider?	N/a

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with the symptoms of CLL affects both the physical and mental health of patients negatively. It can also affect the quality of life of friends, family and carers of the patient. • The significant majority of patients do not believe that the existing CLL treatments available are sufficient. Reasons for this can vary by subgroup, for example fit treatment naive patients want more options as there are currently very few in this setting, whereas r/r patients want more options as they are worried about running out of treatments. There is a strong unmet need for a new treatment in **all** CLL patients and subgroups. • Zanubrutinib has shown to have an improved side-effect profile in trials with comparators and shows improved PFS. As another option for all subgroups, it meets many of the currently unmet needs for CLL patients. • Zanubrutinib also provides another option for those who have cardiovascular co-morbidities, where comparator ibrutinib is unsuitable. • Zanubrutinib is an oral treatment, which is favoured as the preferred mode of delivery for all CLL patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Funding received in 2022 Beigene – none AbbVie - £10,000 AstraZeneca - £11,000 Gilead - £10,000 Janssen - £12,500 Pfizer – 300 Roche – £26,000 (as of June 2022) Sanofi - none
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with CLL. We also used information derived from the 2022 Lymphoma Coalition Global Report on CLL: 2022_Lymphoma_Coalition_Report_CLL_VF_A4_Digital.pdf (lymphomacoalition.org)

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As Chronic Lymphocytic Leukaemia (CLL) is a slow-growing disease, there is rarely a need for urgent treatment and many people don't have treatment for years. Most people first diagnosed with CLL are placed on Active Surveillance (aka Watch and Wait). This can be emotionally challenging for patients - one patient said that *"to live with CLL (means) every day you know you cannot be cured of this cancer."* CLL patients are prone to relapsing and, as CLL is incurable, patients will often be thinking about their next treatment and worrying about how they will respond. Another patient acknowledged the emotional impact of living with CLL and the toll the incurability has on one's life. *"After the initial shock of diagnosis it took me nearly a year to accept, understand and stop worrying about the disease when I was put on watch and wait and not receiving treatment. I think that the effect on mental health of watch & wait is immense as family/friends etc don't understand why you are not having treatment and then disregard the fact that you are experiencing symptoms which can be quite debilitating. It has affected me in that I do suffer from fatigue and sometimes even although I want to go on a long hike I have to accept that I'm more likely to hit a wall these days."* According to the Lymphoma Coalition 2022 report on CLL, the top five reported symptoms were fatigue (65%), abnormal painless swellings (37%), and frequent or repeated infections, shortness of breath, and bruising/bleeding (29% each). Fatigue was a major concern for all patients with CLL/SLL, regardless of if they had been treated or not. Fatigue has a massive impact on many patients' quality of life. A CLL diagnosis also impacts families and carers. One patient noted that her *"husband worries that he will bring infections home to me from the secondary school where he works, particularly during covid before the availability of anti-virals. We still look after the grandchildren a lot but they accept that I may get too tired to do some activities."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Treatment of CLL is complex and completely depends on the individual – their stage of disease, age, symptoms etc. Many people will not have symptoms when first diagnosed and may not need immediate treatment and therefore will be on 'Watch and Wait.' According to the Lymphoma Coalition CLL report, the medical issues reported by patients with CLL are commonly reported treatment-related side effects, highlighting the continued need for better treatment options with fewer toxicities. When patients were asked to rank the importance of outcomes relating to treatment, 'a cure' ranked first (58%), but 'quality of life' (45%) and 'fewer side effects to tolerate' (45%) ranked second and third, respectively. Additionally, except for nausea and vomiting (mostly experienced while in therapy), each of the top treatment related side effects were reported for eight or more years by at least 7% of patients who experienced them. Nearly a fifth (17%) of those who experienced fatigue reported experiencing it for more than eight years. Side effects can impact quality of life and well-being. The majority of patients (60%) who experienced treatment related side effects reported that their everyday activities were negatively impacted as a result: 38% were unable to work or adjusted their working pattern; 44% reported that their social life was negatively impacted; and 23% reported a negative impact on relationships.
8. Is there an unmet need for patients with this condition?	Whilst treatment for CLL is often effective, it is very common for it to relapse. There is an unmet need for a cure for CLL and a treatment that puts people into remission for as long as possible. One patient said that there is an unmet need as the *"mental impact of a cancer diagnosis and then being on watch & wait is not addressed. For a healthcare professional to tell you that you have 'a good cancer' and to 'just forget about it and carry on with your life' is totally underestimating the effect on all areas of a patient's life!"*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Additional options are always beneficial, particularly in the relapsed or refractory space. It is incredibly important to have multiple options for CLL patients as there is a wide range of experiences and preference.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There remains a lack of options for the population considered to be 'fit.' The only treatment options available routinely are FCR and BR but even their use is declining. There is also a need for a BTK inhibitor in this population.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A CLL diagnosis has a significant impact on the quality of life of patients. • There is an unmet need for a cure for CLL and a treatment that puts people into remission for as long as possible. • Multiple options for treatment are always preferred. Everyone's experience of CLL is individual.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NoSingle Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK CLL Forum and the British Society for Haematology (BSH)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK CLL Forum is a charity and is an umbrella organisation for CLL in the UK, bringing together and bridging gaps between scientists, clinicians and patients. It provides a framework within which the entire UK CLL community can input into issues such as guidelines, clinical trials and translational science. BSH promotes excellence in the study, research, and practice of haematology for the benefit of professionals and the wider public.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes – CLL Forum
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Company	Meeting	Amount
AstraZeneca	Both	£10,000
AbbVie	March	£5,000
Roche	March	£2,500
Janssen	March	£3,500
BeiGene	March	£5,000
AbbVie (additional – Medical)	March	£1,000
Roche	October	£2,500
BeiGene	October	£5,000
AbbVie (plus Medical)	October	£7,000
Janssen	October	£3,500
Janssen	October – Additional Virtual Pass	£300.00
AbbVie Medical	October – Additional In Person Pass	£500.00
	TOTAL	**£45,800**

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	*CLL is a cancer characterised by uncontrolled proliferation of lymphocytes within the bone marrow and/or lymph nodes. This leads to progressive bone marrow failure and/or worsening lymphadenopathy. The aim of treatment is to induce remission by clearing disease within the bone marrow and nodes and improve both progression free and overall survival. There is no cure currently for CLL and treatments have limited efficacy and associated toxicities.* A regime with greater efficacy leads to resolution and maintenance of normal marrow function, control of lymphadenopathy and improved overall survival. In addition, as survival improves, the impact of therapies on longer term effects such as secondary cancer, cardiovascular health and Richter's transformation are increasingly important.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	*Response in CLL is measured by the internationally standardised IWCLL criteria (International Workshop on Chronic Lymphocytic Leukaemia). It is generally accepted that partial or complete responses are acceptable, provided they are accompanied with resolution of CLL-related symptoms* *We look for resolution of lymphadenopathy and bone marrow function and with some therapies we also look for very deep remissions in the blood and bone marrow, using flow cytometry or next generation sequencing.*
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The unmet need most relevant to this appraisal is the lack of NICE approved targeted agents for patients in front line, who would be otherwise considered fit for chemoimmunotherapy (CIT) and have non-disrupted TP53 status. To date, these patients can only access fixed-duration Venetoclax-Obinutuzumab and have no access to BTKis. The treatment of CLL patients who fail all existing and available drug-classes, however, is perhaps the biggest unmet need. Despite the recent approval of novel agents for treatment of CLL, which are now readily available in the treatment pathway, there is still a significant subgroup of patients for whom treatment options are exhausted and who die of progressive CLL.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	**<u>UNTREATED CLL</u>** *Recommendations (NICE approved), from latest UK BCSH Guidelines:* • Venetoclax-obinutuzumab (VenO) or acalabrutinib are recommended and NICE-approved options as initial therapy in patients unsuitable for CIT irrespective of TP53 status • *Bendamustine or chlorambucil-based CIT are no longer recommended.* • *NICE-approved treatment options for fit patients with TP53 disruption include acalabrutinib, ibrutinib or venetoclax monotherapy for those with a contra-indication to B-cell receptor inhibitor.* • *Acalabrutinib is recommend for patients who have intact TP53 and for whom FCR or BR are considered unsuitable.* • *For fit patients with intact TP53, VenO may be obtained via CDF.* • *For fit patients with intact TP53 and with mutated IGHV, chemo-immunotherapy with FCR remains an acceptable initial therapy* • *Idelalisib with rituximab (17p deletion or TP53 mutation)* *Recommendations (not NICE approved):* • Acalabrutinib-obinutuzumab is a frontline treatment option or all patients with or without TP53 disruption • Ibrutinib monotherapy is a frontline treatment option for all patients with or without TP53 disruption *Subject to ongoing NICE appraisal:* • Ibrutinib with venetoclax • Zanubrutinib **<u>RELAPSED and refractory CLL</u>**

	Recommendations (NICE approved), from latest UK BCSH Guidelines: • Targeted inhibitors (BTKi or BCL2i alone or in combination with rituximab) are the treatment of choice for relapsed CLL. In England and Wales, ibrutinib, acalabrutinib, and venetoclax with or without rituximab are currently approved and commissioned for this indication. • For patients relapsing after BTKi offer venetoclax-based regimens, irrespective of *TP53* status. • For patients relapsing following fixed-duration venetoclax-based therapy consider either a BTKi or venetoclax retreatment depending on duration of PFS1. • For relapsed patients who are intolerant to ibrutinib, offer either venetoclax-based therapy or acalabrutinib depending on the reason for intolerance. • Idelalisib–rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment. (GRADE IIB). • Patients with double refractory CLL after BTKi and BCL2i should be considered for clinical trials *Subject to ongoing NICE appraisal:* • Zanubrutinib *May also be able to access Pirobrutunub currently on compassionate access scheme if pre-exposed to all other agents*
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	• Schuh AH, Parry-Jones N, Appleby N, Bloor A, Dearden CE, Fegan C, et al. Guideline for the treatment of chronic lymphocytic leukaemia: a British Society for Haematology Guideline. *Br J Haematol*. 2018; **182**(3): 344– 59. • Chloe Pek Sang Tang, Gregory Y.H. Lip, Terry McCormack, Alexander R. Lyon, Peter Hillmen, Sunil Iyengar, Nicolas Martinez-Calle, Nilima Parry-Jones, Piers E.M. Patten, Anna Schuh, Renata Walewska, on behalf of the BSH guidelines committee, UK CLL Forum Management of cardiovascular complications of bruton tyrosine kinase inhibitors. *British Journal of Haematology,* 2022; **196**: 70-78.

	• Eyre TA, Riches JC, Patten PEM, Walewska R, Marr H, Follows G, et al. Richter transformation of chronic lymphocytic leukaemia: a British Society for Haematology Good Practice Paper. *Br J Haematol*. 2022; **196**(4): 864– 70. • Clinical Practice Guidelines – Chronic Lymphocytic Leukaemia (esmo.org) • iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL | Blood | American Society of Hematology (ashpublications.org)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Untreated CLL: In patients fit for CIT the only treatment option recommended and available at present in the UK is Ven-O. Zanubrutinib would offer an excellent alternative, especially for those patients with high risk disease in terms of p53 deletion and mutation, and for those with an unmutated IgHV gene whose PFS is significantly shorter on Ven-O in clinical trials. In pts eligible for Ibrutinib as first line therapy, Zanubrutinib would be preferred in pts with a history of Atrial Fibrillation or other cardiac issues and has lower rates of discontinuation and adverse events. As PFS benefit has been demonstated compared with Ibrutinib In the R/R setting, it seems likely that this benefit may also be demonstrated in the first-line setting. In the UK, we would be able to collect prospective data in this setting, especially for the high risk patients and compare with an historical Blueteq high-risk cohort. Direct comparison with Acalabrutinib for less fit patients in the upfront setting is not available from clinical trials. Relapse/ refractory CLL: Zanubrutinib would be used almost interchangeably with Acalabrutinib or Ibrutinib in this setting. The optimal sequencing of therapy is yet to be determined. The ALPINE trial clearly demonatrated that patients on Zanubrutinib have improved PFS and reduced AEs compared with patients on Ibrutinib.
9c. What impact would the technology have on the current pathway of care?	If made available for patients fit for CIT in the front-line setting this will meet an unmet need in this patient group, with the most favourable side effect profile of any TKI. In the relapse/ refractory setting, superiority has been clearly demonstrated in terms of tolerability and PFS across all ages and all patient subgroups in the ALPINE trial. Zanubrutinib also demonstrates superiority for high risk patients as compared to Ibrutinib, A previous trial (ELEVATE RR) did not demonstrate this for Acalabrutinib vs Ibrutinib; suggesting that Zanubrutinib may be the TKi of choice for those with p53 disruption.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Zanubrutinib will be used in the same way and on the same clinical delivery pathways as the existing TKis.
10a. How does healthcare resource use differ between the technology and current care?	A small number of younger patients would be able to access continuous therapy rather than time-limited Ven-O; but these patients are likely to cycle across all treatments and future trials may inform both optimal sequencing and intermittent BTKi use.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Haematology Clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None –other BTKis already in routine use
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In the upfront setting, we do not yet have any direct comparison between Ven-O and BTKi, but there is limited evidence to suggest that patients with high risk disease – p53 deletion/ mutation – have longer PFS on BTKi, with younger patients in the UK accessing Ibrutinib in this scenario. Zanubrutinib will definitely lead to less cardiac events and discontinuations in this young patient group and it appears that sudden cardiac death is reduced on this drug. Also, young patients with an unmutated IgHV gene have shorter PFS on Ven-O and cannot currently access a BTKi. Zanubrutinib also demonstates superiority over ibrutinib in this patient group in the R/R setting in the Alpine trial,
11a. Do you expect the technology to increase length of life more than current care?	Overall survival data in R/R setting is not yet mature, so the impact on OS of reducing adverse effects and maximising the number of patients remaining on Zanubrutinib remains to be demonstrated.

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Cardiovascular (CV) adverse events associated with BTKi therapy may interfere with continuation of best possible care, induce life-threatening CV complications or lead to long-term morbidity including worse CLL-related outcomes if optimal BTKi treatment is withheld. A BTKi such as Zanubrutinib with a lower risk of development of AF and a reduced risk of sudden cardiac death is likely to bring significant quality of life benefits.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Evidence that Zanubrutinib is superior to Ibrutinib across all patient sub-groups. It is likely to be especially beneficial for patients with pre-exicsting cardiac issues.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	BTKis, already in regular use so unlikely to be any new issues.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Currently, the technology is continued until CLL progresses.

include any additional testing?	The STATIC trial (in set up in the UK) will address whether intermittent treatment is beneficial in patients on Ibrutinib.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Benefit in terms of reduction in adverse events should be captured. The long-term impact of the reduction in cardiovascular events of long term health and CLL treatment mey be difficult to model.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is the second generation of the innovative BTKis, bringing increased efficacy with a reduction in side effects, but not with any additional innovation in the mode of action.
16a. Is the technology a 'step-change' in the management of the condition?	It would be a step-change to make a BTKi available as a first treatment to young patients with or without p53 deletion or mutation, with an optimal side effect profile. In addition, in the relapse setting, minimising the cardiac side effect profile of mediciation will have a significant effect on quality of life.
16b. Does the use of the technology address any particular unmet need of the patient population?	As above.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This technology has a much better side effect profile than existing treatments.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	In the R/R setting, the randomised phase 3 ALPINE R/R trial is comparable with UK clinical practice, comparing Zanubrutinib to Ibrutinib (currently available in this setting in the UK) in patients who had received at least one course of therapy. At 24 months, PFS was superior in the investigational arm (78.4% vs 65.9% p=0.002). In addition, Zanubrutinib had improved PFS across all subgroups, including those with p53 deletion or mutation. Overall response was higher and discontinuation rates lower; with a reduction in cardiac events and deaths in Zanubrutinib patients. Data in untreated patients compared Zanubrutinib to R-Bendamustine. This was an appropriate comparator with UK practice at the time of the SEQUIA trial design in patients >65, or not fit enough for FCR. Median PFS was not reached (95% CI: NE, NE) in the zanubrutinib cohort compared with 33.7 months (95% CI: 28.1, NE) in the BR cohort (HR= 0.42, 95% CI: 0.28, 0.63; p=<0.0001). Since the positive NICE appraisals for Ven-O and Acalabrutinib, however, it now very rare for CIT to be offered as first line therapy. In addition, in fit and young patients, we know that Ibrutinib is superior to both R-Bendamustine and FCR (the previous gold standard therapy) in a Phase 3 upfront setting. Given that we see reduced arrhythmic adverse effects, reduced discontinuations and improved PFS in the R/R setting with Zanubrutinib vs Ibrutinib in CLL (and in

	all settings in other B-cell malignancies) it seems likely that Zanubrutib will also be a superior BTKi in the front-line setting and afford significant benefit to our young patients in the UK, who cannot currently access a BTKi. Finally, in both settings, there is some limited evidence that Zanubrutinib is better tolerated even in patients who have had issues on Acalabrutinib.
18a. If not, how could the results be extrapolated to the UK setting?	As above
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	More relevant to review findings in the R/R setting as the Alpine trial directly compared BTKis: • At a median of 29.6 months Zanubrutinib is superior to Ibrutinib in all subgroups in terms of overall response and PFS. • PFS at 24 months in pts with p53 deletion or mutation was 72.6% on Zanubrutinib vs 54.6% on Ibrutinib, Of note, the ELEVATE RR trial did not observe benefit for Acalabrutinib over Ibrutinib in this patient population, suggesting superior efficacy for Zanubrutinibin this sub-group • Treatment discontinuation rate was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%) allowing an increase in the number of patients able to benefit from this line of therapy • Discontinuation rates due to cardiac disorders were 0.3% on Zanubrutinib vs 4.3% on Ibrutinib • Rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% vs 13.3%) • No grade 5 AEs due to cardiac disorders with zanubrutinib vs 6 (1.9%) with ibrutinib
18c. If surrogate outcome measures were used, do they adequately predict	Not applicable

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA796 689, TA561, TA429 and TA359?	TA796 • Not aware of any updates since recent appraisal TA689 • Not aware of any published updates TA561: • Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. Blood. 2022;140(8):839-850. TA429 • Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Kipps TJ, Moreno C, Montillo M, Burger JA, Byrd JC, Hillmen P, Dai S, Szoke A, Dean JP, Woyach JA. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019 Dec;94(12):1353-1363. TA359: • Paolo Ghia, Steven E. Coutre, Bruce D. Cheson, Jacqueline C. Barrientos, Peter Hillmen, Andrew R. Pettitt, Andrew D. Zelenetz, Sanatan Shreay, Michael Hallek, Richard R. Furman. Impact of idelalisib on health-related quality of life in patients with relapsed chronic lymphocytic leukemia in a phase III randomized trial. Haematologica 2020;105(10):e51
21. How do data on real-world experience	There is limited real-world data on Zanubrutinib in CLL as it has only just received its FDA/ MHRA approval.

compare with the trial data?	An abstract compared BTKis retrospectively in a comparable B-cell malignancy, Mantle Cell Lymphoma (MCL), The study reviewed 300 patients; (3x100 exposed to each of zanubrutinib, ibrutinib or acalabrutinib) outside of clinical trials. Whilst patients treated with zanubrutinib were older and had more complex MCL baseline features at initiation, multivariable regression suggested a trend favouring zanubrutinib over ibrutinib or acalabrutinib for both response and adverse events. *Real-world (RW) treatment patterns and comparative effectiveness of Bruton tyrosine kinase inhibitors (BTKi) in patients (pts) with mantle cell lymphoma (MCL).* *Bijal D. Shah, Keri Yang, Andrew J. Klink, Tom Liu, Todd M. Zimmerman, Ajeet Gajra, and Boxiong TangJournal of Clinical Oncology 2022 40:16_suppl, e18727-e18727*

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The drug should be made available to all age groups. Equality of access should be easy to achieve as this is an oral medication.
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Zanubrutinib is a very effective second generation BTKi which demonstrates superior efficacy and improved tolerability over ibrutinib. • Significantly fewer patients need to discontinue therapy due to adverse effects. This means that more patients respond and benefit on this line of therapy, in a disease where we still have limited treatment options. • No sudden cardiac deaths seen on Zanubrutinib in either trial. • Deliverable to patients of all ages and levels of fitness. • Excellent PFS in high risk disease compared with other currently available therapies

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Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Produced by Newcastle University

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None

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Tara Homer acted as project lead. Andrew Bryant acted as lead effectiveness reviewer. Giovany Orozco-Leal acted as lead health economist. Sonya Garcia Gonzalez-Moral acted as lead reviewer of the literature search methods. Nick Meader reviewed the matching-adjusted indirect comparison. Eugenie Evelynne Johnson and Oluwatomi Arisa acted as assistant effectiveness reviewers. Tumi Sotire, Nawaraj Bhattarai, Laura Ternent and Sedighe Hosseinijebeli acted as assistant health economics reviewers. Claire Eastaugh assisted in reviewing the literature search methods. Luke Vale assisted in reviewing the literature search methods, the effectiveness section and the health economics section.

Abbreviations

AE	Adverse event
AIC	Akaike's Information Criterion
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
BCL2i	B-cell lymphoma 2 inhibitor
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine-rituximab
BSA	Body surface area
BSH	British Society for Haematology
BTKi	Bruton tyrosine kinase inhibitor
CC	Complication and comorbidity
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
ChlorO	Chlorambucil-obinutuzimab
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CIT	Chemoimmunotherapy
CLL	Chronic lymphocytic leukaemia
CLL-IPI	Chronic lymphocytic leukaemia international prognostic index
CMA	Cost minimisation analysis
CR	Complete response
CRi	Complete response with incomplete bone marrow recovery
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost-utility analysis
DCO	Data cut-off
del17p	Deletion of the short arm chromosome 17
DMC	Data Monitoring Committee
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EHA	European Haematology Association
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FACT	Functional Assessment of Cancer Therapy
FCR	Fludarabine, cyclophosphamide and rituximab
FE	Fixing errors
FISH	Fluorescence in situ hybridisation
FV	Fixing violations
GHS	Global health score
GI	Gastrointestinal
HBcAB	Hepatitis B core antibody

HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health State Utility Value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICML	International Conference on Malignant Lymphoma
IGHV	Immunoglobulin heavy chain gene
INAHTA	The International Network of Agencies for Health Technology Assessment
INV	Investigator
IPD	Individual patient-level data
IPI	International prognostic index
I-R	Idelalisib plus rituximab
IRC	Independent Review Committee
ISPOR	Professional society for health economics and outcomes research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
LS	Least squares
LY	Life year
LYG	Life years gained
Kg	Kilogram
m	Metre
MAIC	Matching-adjusted indirect comparison
medDRA	medical Dictionary of Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MJ	Matters of judgement
ml	millilitre
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NA	Not applicable
NE	Not estimable
NHL	Non-Hodgkin's Lymphoma
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nPR	Nodular partial remission
NR	Not reported
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PD	Progressed disease
PF	Progression-free
PfC	Point for clarification
PFS	Progression-free survival
PH	Proportional hazard
PICOS	Patient, intervention, comparison, outcome, study design
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival
PRESS	Peer Review of Electronic Search Strategies

PRL	Partial response with lymphocytosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dosing intensity
RR	Relative risk; Risk ratio
R/R	Relapsed or refractory
SAE	Serious adverse events
SCHARRHUD	School of Health And Related Research Health Utility Database
SD	Standard deviation
SE	Standard error
SLL	Small lymphocytic leukaemia
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology assessment
TEAE	Treatment-emergent adverse event
TLS	Tumour lysis syndrome
TN	Treatment-naïve
TP53	Tumour protein P53 gene
TTD	Time to death
TTP	Time to progression
TTTD	Time to treatment discontinuation
TTTF	Time to treatment failure
UI	Utility index
UK	United Kingdom
URL	Uniform resource locator
USA	United States of America
VAS	Visual analogue scale
VenO	Venetoclax-obintutuzumab
VenR	Venetoclax-rituximab
1LTx	First-line treatment
2LTx	Second-line treatment

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1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

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Key issue [2]	Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL	3.1.1
Key issue [3]	Applicability of the SEQUOIA trial population to the untreated CLL comparison	2.5, 3.2.1.1, 3.6, 4.3.3, 4.3.6.2.1, 6.2.6
Key issue [4]	Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL	3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2
Key issue [5]	Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL	4.1.1
Key issue [6]	Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2, 6.2.1, 6.3.1
Key issue [7]	Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	4.3.8, 4.4.8, 6.2.2, 6.3.2
Key issue [8]	Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	4.3.6.1, 4.4.6.1, 6.2.2, 6.2.6,6.3.2
Key issue [9]	Uncertainty in untreated "high-risk" CLL subgroup	4.3.3, 4.3.6.2.3, 6.2.6
Abbreviations: CLL = Chronic lymphocytic leukaemia; CMA = Cost-minimisation analysis; MAIC = Matching-adjusted indirect comparison		

1.2 Overview of key model outcomes

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue [1] – Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL

Report section	2.3, 3.5.1
Description of issue and why the EAG has identified it as important	The NICE decision problem lists venetoclax-rituximab (VenR) as a relevant comparator to zanubrutinib in the R/R CLL population. However, the CS excluded VenR as a relevant comparator in this population; the company stated that VenR would not be recommended in patients who have not previously received treatment with a BTKi, the population eligible for zanubrutinib.

Report section	2.3, 3.5.1
	However, the most recent British Society for Haematology (BSH) guidelines recommend VenR as a treatment for R/R CLL patients. Furthermore, the EAG's clinical advisor disagreed with the perspective of the company, as there would be some patients who would previously have received chemoimmunotherapy (CIT) for whom a BTKi would be a second-line option. Consequently, the EAG has concerns that VenR has been erroneously excluded as a relevant comparator from the decision problem. This omission means there is uncertainty in the results of both the clinical effectiveness and cost-effectiveness model of R/R CLL, as zanubrutinib has not been compared against VenR.
What alternative approach has the EAG suggested?	The EAG undertook an NMA using the data from the SLR and TA561 to generate effectiveness estimates for VenR. The results were: PFS HR = 1.48 (95% CI 0.49, 4.45); and OS HR = 1.87 (95% CI 0.59, 5.91). Based on the point estimates, VenR is more effective than zanubrutinib but, given the wide confidence intervals, the EAG cannot draw firm conclusions on the effectiveness and hence cost-effectiveness of VenR. This limitation is compounded because the EAG have concerns that the search strategy used to identify evidence for VenR may not be sufficient.
What is the expected effect on the cost-effectiveness estimates?	The effect of including VenR as a comparator in the R/R model on the cost-effectiveness of zanubrutinib was not estimated due to the uncertainty in the effectiveness estimate derived by the EAG. If VenR is less costly and more effective than zanubrutinib then zanubrutinib is unlikely to be considered cost-effective in this comparison. However, if VenR is more costly than zanubrutinib and if zanubrutinib was as effective or more effective than VenR, it is likely that zanubrutinib would be considered cost-effective.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggest there are several factors that might help resolve this key issue. Firstly, if the company's submission was updated to ensure all relevant data, including clinical trial data, on the effectiveness of VenR was extracted from the SLR. Secondly, these data could be used to conduct an unanchored MAIC comparing VenR and zanubrutinib, which would reduce the uncertainty in the estimates derived by the EAG. Thirdly, the updated effectiveness estimates of VenR could then be incorporated into the economic model of R/R CLL, in line with the decision problem, to estimate the cost-effectiveness of zanubrutinib compared with VenR.
Abbreviations: BTKi = Bruton tyrosine kinase inhibitor; CIT = Chemoimmunotherapy; CLL = Chronic lymphocytic leukaemia; CI = Confidence interval; CS = Company submission; EAG = Evidence Assessment Group; MAIC = Matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; R/R = Relapsed or refractory; SLR = Systematic literature review; VenR = Venetoclax-rituximab.	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.3: Key issue [2] – Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL

Report section	3.1.1
Description of issue and why the EAG has identified it as important	All searches for the identification of clinical studies lacked sensitivity and were limited to English language only. did not consider a comprehensive range of grey literature sources, and did not search for ongoing clinical trials in trial registries. Despite alignment with the NICE methods guidance (PMG36) there are concerns with the currency of the evidence presented as searches were conducted at least nine months ago. Furthermore, the company report two study design filters, one for RCTs and one for observational studies, but provide no supporting information as to the rationale for modifying the published filter, meaning the EAG are unable to verify their integrity.
What alternative approach has the EAG suggested?	The approach for the identification of clinical trials via conference papers indexed in Embase does not appear robust enough; modifications to the presented search strategy to explicitly search for those identified conferences as well as additional hand searching of conference sites should be conducted. The Embase.com search strategy should include more alternative drug names and codes for maximising the sensitivity of the searches for interventions. Additionally, in non-bibliographic databases (e.g. NICE and SMC websites) the alternative spelling and search terms for CLL should be used. There are validated RCT filters that maximise the sensitivity that should also be used.
What is the expected effect on the cost-effectiveness estimates?	The EAG could not ascertain if increased evidence would increase or reduce the incremental cost-effectiveness ratios (ICERs).
What additional evidence or analyses might help to resolve this key issue?	The EAG suggest there are several factors that might help resolve this key issue. Firstly, the company could perform more extensive and comprehensive searches that consider up-to-date sources. Secondly, conference papers where results of ongoing studies may have been disseminated ahead of publication of the peer-review papers should be considered. A more robust search of the literature would help to ensure all relevant clinical trial data are identified. Thirdly, the MAIC could then be updated if any additional data were identified which may potentially reduce uncertainty in the effectiveness of ibrutinib, acalabrutinib and zanubrutinib.
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; NICE = National Institute of Health and Care Excellence; UK = United Kingdom; RCT = Randomised controlled trial; SMC = Scottish Medicine Consortium.	

Table 1.4: Key issue [3] – Applicability of the SEQUOIA trial population to the untreated CLL comparison

Report section	**2.5, 3.2.1.1, 3.6, 4.3.3, 4.3.6.2.1, 6.2.6**
Description of issue and why the EAG has identified it as important	The company defined "unfit" patients with CLL as those who would be unsuitable for treatment with FCR and BR (CS Figure 1). Later, in the CS the company defines "unfit" patients with CLL as those unsuitable for FCR or BR. The CS also states that there was a lack of clinical trial data for "fit" participants, so they did not present an assessment of this population. However, in Cohort 1 of the key SEQUOIA trial of untreated CLL participants were randomised to either zanubrutinib or BR. By the company's definition, this means participants in SEQUOIA Cohort 1 would have been considered "fit." Furthermore, the current BSH guidelines state that CIT, such as BR, is only considered for patients with untreated CLL and intact TP53 who are deemed to be "fit" and should be considered as an acceptable alternative for "fit" patients in whom FCR is contraindicated. As such, participants in SEQUOIA Cohort 1 can be considered "fit" by the standards of the BSH guidelines and the company's definition. The EAG sought clinical advice on the definitions of "fit" versus "unfit." The EAG acknowledge that the definition of "fitness" is non-binary and that the SEQOUIA trial recruited patients who were 65 years and older and were not "fit" for intensive CIT. However, based on the company's placement of zanubrutinib in the clinical pathway (CS Figure 1), the EAG has concerns about the categorisation of participants in Cohort 1 in SEQUOIA as "unfit" rather than "fit" due to these participants being eligible for BR. Furthermore, the EAG has concerns about data from "fit" participants being used as a proxy for the "unfit" population in the economic model. The EAG are therefore uncertain of the applicability of the effectiveness data from Cohort 1 in SEQUOIA to the "unfit" population.
What alternative approach has the EAG suggested?	The EAG are unable to suggest an alternative approach to this key issue and appreciate that evidence in this population is sparse.
What is the expected effect on the cost-effectiveness estimates?	The EAG is uncertain of the impact of this issue on the cost-effectiveness estimates of zanubrutinib as there are no data available to determine what the effectiveness of zanubrutinib would be in an "unfit" untreated CLL population.
What additional evidence or analyses might help to resolve this key issue?	Further research undertaken in an "unfit" untreated CLL population in future may help resolve this key issue.

Abbreviations: BR = Bendamustine-rituximab; BSH = British Society for Haematology; CIT = Chemoimmunotherapy; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; FCR = Fludarabine, cyclophosphamide and rituximab.

Table 1.5: Key issue [4] – Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL

Report section	**3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2**
Description of issue and why the EAG has identified it as important	The company claim the non-inferiority of zanubrutinib throughout the CS; the EAG considers this an important issue as this interpretation is pivotal to the justification by the company that the CMA approach adopted for both the untreated CLL and R/R CLL economic models is acceptable (see Key Issue [6]). The EAG consider the company's conclusions in the MAIC analyses confuse a lack of statistical significance with non-inferiority or equivalence. The EAG believe there is insufficient evidence of non-inferiority for: 1) zanubrutinib compared with acalabrutinib in the MAIC analyses in both untreated CLL and R/R CLL and 2) zanubrutinib when naively compared with ibrutinib in untreated CLL, as the upper limit of the 95% CIs included a clinical meaningful difference. The EAG hence consider that a CMA was not an appropriate choice for the cost-effectiveness analyses in these comparisons.
What alternative approach has the EAG suggested?	In terms of the MAIC, the EAG have no suggested alternatives. Given that the assumption of non-inferiority does not hold, the EAG recommend that a CUA should have been undertaken for both economic models.
What is the expected effect on the cost-effectiveness estimates?	The base-case economic models of both untreated CLL and R/R CLL rest on the assumption of non-inferiority of zanubrutinib over ibrutinib and acalabrutinib to justify a CMA approach. Rejecting the non-inferiority assumption would mean a CUA would offer a better representation of the decision problem. In untreated CLL, while it is likely that zanubrutinib would be considered less costly and more effective based on the mean estimates of effectiveness, there is uncertainty in these results and it is expected that the probability zanubrutinib being considered cost-effective would reduce. Similarly, in R/R CLL, when compared to acalabrutinib it is likely that zanubrutinib would still be considered less costly and less effective, but the expected probability of cost-effectiveness would reduce. However, the EAG acknowledge the assumption of non-inferiority in the comparison of zanubrutinib with ibrutinib in the R/R CLL population is conservative. When compared with ibrutinib, it is likely that the probability of zanubrutinib being considered cost-effective would increase.
What additional evidence or analyses might help to resolve this key issue?	None of the analyses in the MAIC demonstrated non-inferiority, hence adopting a CUA approach rather than a CMA would help to resolve this key issue. In the untreated CLL model, this would need to be conducted for both acalabrutinib and ibrutinib. In the R/R CLL model, this would need to be conducted for acalabrutinib only.

Report section	3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2
Abbreviations: CLL = Chronic lymphocytic leukaemia; CMA = Cost-minimisation analysis; CS = Company submission; CUA = Cost-utility analysis; EAG = Evidence Assessment Group; MAIC = Matching-adjusted indirect comparison; R/R = Relapsed or refractory.	

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Table 1.6: Key issue [5] – Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL

Report section	4.1.1
Description of issue and why the EAG has identified it as important	The company undertook one SLR and applied filters to the results on cost-effectiveness, HRQoL, costs and resource use in previously untreated or R/R CLL. As outlined in Key issue [2], the EAG have concerns that the SLR was not sensitive enough to capture all clinical studies of interest. The EAG identified a disagreement between the source of the filters and the actual filters used, with no rationale for the alteration being provided by the company. Hence, the EAG could not be confident that all studies containing utility data were identified from the company's search and the application of filters. In addition, the EAG has concerns that the company did not consider a comprehensive and up-to-date range of grey literature sources to identify utility values and that the search terms used by the company in their additional searches in databases (e.g. ScHARRHUD) were not sufficient to capture all relevant data.
What alternative approach has the EAG suggested?	The EAG suggest that the company should have undertaken a separate systematic review to identify relevant health state utility values (HSUVs). Additionally, more recent sources such as the CEA registry (https://cear.tuftsmedicalcenter.org/) or the INATHA HTA database (https://database.inahta.org/) should be used.
What is the expected effect on the cost-effectiveness estimates?	The EAG could not ascertain if increased evidence would have a negative or positive impact on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	The company should perform separate extensive, comprehensive and current searches on HSUVs in published and unpublished sources. If using a filter for the identification of HSUVs amongst published literature, reporting transparently which filter has been selected and adapted for the platform used to access to databases (e.g. Embase.com) is needed. As is good practice, the company should provide justification for any alterations to published study filters. Furthermore, the company should use unpublished literature sources, such as the CEA Registry and the INATHA databases, to identify additional utility values.
Abbreviations: CEA = Cost-effectiveness analysis; CLL = Chronic lymphocytic leukaemia; EAG = Evidence Assessment Group; HSUV = Health state utility values; HRQoL = Health-related quality of life; HTA = Health Technology Assessment; INHATA = International Network of Agencies for Health Technology Assessment; SLR = Systematic literature review.	

Table 1.7: Key issue [6] – Use of a cost-minimisation analysis as the company's base-case economic model in untreated CLL and R/R CLL

Report section	**3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2, 6.2.1, 6.3.1**
Description of issue and why the EAG has identified it as important	Untreated CLL: The justification given by the company to present a CMA as the base-case approach over a CUA rely on the results from the MAIC generating sufficient evidence of non-inferiority between zanubrutinib and acalabrutinib across previously untreated CLL patients. The EAG does not consider that the MAIC results provide sufficient evidence of non-inferiority (see Key Issue [4]), hence a CUA approach is considered more appropriate to represent the decision problem. Additionally, the company use the assumption that data from those with R/R CLL can be used as a proxy for untreated "high-risk" CLL patients for the comparison of zanubrutinib with ibrutinib. This is a strong assumption given that only 23% of participants in ALPINE had del17p or TP53 mutation. In addition, advice to the EAG suggest that R/R CLL is not a suitable proxy for untreated "high-risk" CLL hence there is a lot of uncertainty in this assumption and the company cannot assume that the effectiveness of zanubrutinib compared with ibrutinib in patients with R/R CLL is also experienced by those with untreated "high-risk" CLL. The company undertook a scenario analysis using data from their naïve comparison however the EAG consider these data to be subject to uncertainty due to the nature of this study being retrospective, and because potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison. R/R CLL: As with untreated CLL, evidence of from the MAIC results was insufficient to convincingly justify a CMA approach between zanubrutinib and acalabrutinib (see Key Issue [4]). However, the EAG acknowledges that a CMA assuming equivalent efficacy between zanubrutinib and ibrutinib has the potential to be conservative, given the results of the ALPINE trial, even though data from ALPINE was considered immature (see Key Issue [8]).
What alternative approach has the EAG suggested?	The EAG considers a CUA, which is recommended by NICE unless evidence of non-inferiority for all outcomes of interest is determined, to be the most appropriate approach to represent the decision problem across both untreated and R/R CLL. However, the EAG acknowledge that a CMA to compare zanubrutinib with ibrutinib in R/R CLL was a conservative assumption by the company.
What is the expected effect on the cost-effectiveness estimates?	The EAG acknowledge that the adoption of a CMA over a CUA may not materially change conclusions, as demonstrated from the EAG's base-case analyses. However, the EAG cannot be certain of this as the company's economic model was structured to undertake a CMA and hence there are limitations associated with the CUAs undertaken by both the company and EAG. Untreated CLL: similar to the company results when a CUA approach was adopted in the EAG base-case zanubrutinib was less

Report section	3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2, 6.2.1, 6.3.1
	costly when compared to acalabrutinib and ibrutinib and more effective in terms of QALYs gained thus making zanubrutinib dominant. R/R CLL: when a CUA approach was adopted, zanubrutinib was less costly and less effective, in terms of QALYs gained, compared with acalabrutinib. Therefore, an ICER was estimated for acalabrutinib as it was more costly and more effective than zanubrutinib. The ICER was £340,019 hence, zanubrutinib is still likely to be considered cost-effective. When compared with ibrutinib, zanubrutinib was less costly and more effective, hence zanubrutinib would be considered the most cost-effective treatment option. However, the EAG scenario analyses results using a CUA for both untreated CLL and R/R CLL populations need to be interpreted with caution as the CUA assumption adopted by the EAG was associated with the following caveats: 1) Only clinical and HRQoL data in the CS were used to populate the models (Key Issues [2], [5] and [7]); 2) Constant hazards were assumed over the model lifetime; 3) There were no differences in treatment discontinuation assumed; 4) VenR was not included as a comparator in the R/R CLL economic model due to uncertainty in the estimates derived by the EAG (Key Issue [1]); 5) There were no longer-term data to inform and validate the choice of parametric survival functions (Key Issue [8]); 6) Clinical data used to inform the untreated CLL model was subject to uncertainty as set out in the Key Issues ([3] and [9]); 7) Time to progression data to inform the untreated "high-risk" CLL subgroup was subject to uncertainty as set out in Key Issue [9].
What additional evidence or analyses might help to resolve this key issue?	Untreated CLL: The company's base-case analysis assumed that all treatments were equivalent in terms of clinical effectiveness and hence did not consider the immaturity or uncertainty in the clinical estimate the utility estimates (see Key Issue [7]). The EAG utilised the data available in the company submission but there is a lack of data on time to disease progression for acalabrutinib; this data could improve the accuracy of the model presented and reduce the uncertainty around the relative effectiveness of zanubrutinib. Moreover, head-to-head data from a clinical trial between zanubrutinib and acalabrutinib, allowing for a subgroup analysis of participants with and without del17p or TP53 mutation, would address most of the uncertainties presented (see Key Issue [9]). Furthermore, data comparing ibrutinib and zanubrutinib in untreated "high-risk" CLL patients is needed as using data from

Report section	3.3, 3.4, 3.6, 4.3.6.2, 4.4.6.2, 6.2.1, 6.3.1
	the R/R CLL clinical trials as proxy is subject to uncertainty (see Key Issue [9]). The company attempted to address this uncertainty by undertaking a scenario analysis using data from their naïve comparison however the EAG consider these data to be subject to uncertainty due to the nature of this study being retrospective, and because potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison. R/R CLL: As with the untreated CLL population, head-to-head data from a clinical trial between zanubrutinib and acalabrutinib would reduce the uncertainty in the clinical and cost-effectiveness results.
Abbreviations: CLL = Chronic lymphocytic leukaemia; CMA = Cost-minimisation analysis; CUA = Cost-utility analysis; del17p = 17p deletion; EAG = Evidence Assessment Group; MAIC = Matching-adjusted indirect comparison; NICE = National Institute of Health and Care Excellence; R/R = Relapsed or refractory.	

Table 1.8: Key issue [7] – Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL

Report section	4.3.8, 4.4.8, 6.2.2, 6.3.2
Description of issue and why the EAG has identified it as important	The base-case economic models for both untreated CLL and R/R CLL presented by the company does not use utility values collected from the trials that inform clinical effectiveness parameters (the SEQUOIA trial for untreated CLL and the ALPINE trial for R/R CLL). The company argued that these values lacked face validity, as they were too high when compared to utility values from the age-sex matched general population. Therefore, the company used UK general population age-sex matched utility values for the progression-free (PF) health state and literature values (Holzner *et al*., 2018) for the progressed disease (PD) health state. No scenario analyses were undertaken to address the uncertainty in these utility estimates. However, the EAG acknowledges that the company were unlikely to undertake scenario analyses in these estimates given that they used the CMA approach as their base-case, which, in the EAG's opinion, was erroneous (see Key Issues [4 and 6]). In the company base-case, it was assumed there were no differences in QALYs between the treatments; utility values were only considered in a scenario analysis. The cost-effectiveness results from both the untreated and R/R CLL models were sensitive to changes in utility values when a CUA approach was chosen, hence the EAG considers the uncertainty in the utility estimates to be a key issue that was not explored in the CS.
What alternative approach has the EAG suggested?	The EAG considers that a deeper exploration of alternative utility values on the cost-effectiveness of zanubrutinib is important to reflect the impact of this uncertainty. Therefore, the EAG has implemented a series of scenario analyses to report how alternative utility values affect the results.

Report section	4.3.8, 4.4.8, 6.2.2, 6.3.2
What is the expected effect on the cost-effectiveness estimates?	The EAG base-case maintains the utility values from the CS base-case. However, the EAG scenarios explored using utility values from SEQUOIA and alternative PD disutility values. In the untreated CLL model when using utility values derived from the SEQUOIA trial the average total QALYs for both zanubrutinib and acalabrutinib were lower than those estimated in the EAG base-case. Zanubrutinib was less effective than acalabrutinib ([redacted]). However, zanubrutinib would still be considered cost-effective as the ICER associated with acalabrutinib was over £28 million. When compared with ibrutinib, zanubrutinib was dominant as it was less costly and more effective. Alternative changes to utility values in the untreated models for both pairwise comparisons maintained these conclusions. In the R/R CLL model when using utility values derived from the ALPINE trial the average total utility difference between zanubrutinib and acalabrutinib increased, and zanubrutinib was less effective in terms of QALYs gained ([redacted]). The conclusions did not change from the EAG base-case in that zanubrutinib was still the preferred treatment option as the ICER associated with acalabrutinib was in excess of £250,000. Both the untreated and R/R CLL economic models were particularly sensitive to changes to utility values assigned to the PD health state. Higher utility values in the PD health state decreased the overall QALY gains across all arms in both models. However, because of the cost-savings associated with zanubrutinib changes to utility values had a minimal effect on overall conclusions.
What additional evidence or analyses might help to resolve this key issue?	A targeted literature review may identify alternative utility values which could be used in the economic model (see Key Issue [5]). Furthermore, data directly elicited from patients during progressed disease would help reduce this uncertainty.
Abbreviations: CLL = Chronic lymphocytic leukaemia; CMA = Cost-minimisation analysis; CS = Company submission; CUA = Cost-utility analysis; EAG = Evidence Assessment Group; HRQoL = Health-related quality of life; QALY = Quality-adjusted life year; R/R = Relapsed or refractory.	

Table 1.9: Key issue [8] – Immaturity of trial data and parametric survival functions for untreated CLL and R/R CLL

Report section	4.3.6.1, 4.4.6.1, 6.2.2, 6.2.6,6.3.2
Description of issue and why the EAG has identified it as important	Untreated CLL: The economic model follows a life-time horizon with a 30-year duration, which the EAG considers appropriate for the decision problem. By comparison, the follow-up data available from the SEQUOIA trial used in the economic model is relatively short (SEQUOIA arm A follow-up = 26.35 months; SEQUOIA arm C follow-up = 30.52 months), coupled with data immaturity from low event numbers for key outcomes such as OS. Hence, the

Report section	4.3.6.1, 4.4.6.1, 6.2.2, 6.2.6,6.3.2
	economic model relies on parametric models to predict the survival curve of key outcomes over the long-term. Results in the untreated CLL economic model were sensitive to predictions of time to disease progression. R/R CLL: As with the untreated CLL model, follow-up data from the key trial is short relative to the 30-year time horizon of the economic model (ALPINE zanubrutinib arm follow-up = 24.34 months; ibrutinib follow-up = 23.82 months). This economic model also followed a partitioned survival structure, which makes the results particularly sensitive to predictions of PFS and OS. The absence of real-world evidence outside the trials presented across both models makes the selection of survival models heavily reliant on clinical expert opinion.
What alternative approach has the EAG suggested?	The EAG suggests further exploration of alternative survival curves across both models to assess the impact of model selection and long-term predictions of survival on cost-effectiveness. The EAG note that the company applied alternative survival curves to both PFS and OS as part of their scenario analyses.
What is the expected effect on the cost-effectiveness estimates?	For both the untreated CLL and R/R CLL models the application of alternative survival models to OS and PFS did change the incremental results for costs and QALYs but overall the conclusions from the EAG base-case did not change. zanubrutinib was less costly and more effective than acalabrutinib in untreated CLL and ibrutinib in untreated CLL and R/R CLL. In R/R CLL when compared with acalabrutinib, zanubrutinib was less costly and less effective. However, the ICER associated with acalabrutinib for all scenario analyses was in excess of £250,000 hence zanubrutinib would be considered the preferred treatment option.
What additional evidence or analyses might help to resolve this key issue?	Longer-term data from both of the SEQUOIA and ALPINE trials would decrease the uncertainty in key clinical outcomes in untreated CLL and R/R CLL. Furthermore, real-world evidence is needed to assess the accuracy of the models used.
Abbreviations: CLL = Chronic lymphocytic leukaemia; EAG = Evidence Assessment Group; OS = Overall survival; PFS = Progression-free survival; R/R = Relapsed or refractory.	

Table 1.10 Key issue [9] – Uncertainty in untreated "high-risk" CLL subgroup

Report section	4.3.3, 4.3.6.2.3, 6.2.6
Description of issue and why the EAG has identified it as important	As per the NICE scope, if available, data from subgroup analyses for those with del17p or TP53 mutation ("high-risk") in the untreated CLL population should be presented. According to the treatment pathway "high-risk" patients are eligible for ibrutinib or acalabrutinib. The company had data on the effectiveness of zanubrutinib in "high-risk" patients (Cohort 2) from SEQUOIA. However, data

Report section	4.3.3, 4.3.6.2.3, 6.2.6
	for acalabrutinib were only available for a population combining both "high-risk" and non "high-risk" groups. The lack of disaggregated data did not allow for a MAIC comparing zanubrutinib in the untreated "high-risk" CLL subgroup. Therefore, subgroup-specific differences in the relative effectiveness and hence cost-effectiveness of zanubrutinib compared with acalabrutinib are still uncertain. In addition, the data available for untreated "high-risk" CLL patients comparing zanubrutinib with ibrutinib was based on the ALPINE trial, which was undertaken in an R/R CLL population with only 23% of participants being considered "high-risk" (i.e., had del17p or TP53 mutation). The company also used data from their naïve comparison however, the EAG have concerns about the validity of this data due to the nature of this study being retrospective, and where potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison.
What alternative approach has the EAG suggested?	The EAG suggest that the company should try and determine if the data on the effectiveness for acalabrutinib in untreated "high-risk" CLL can be identified. If there are data available by risk subgroup, then the company's scenario analysis should be updated to reflect the effect of acalabrutinib in these populations. Even though this data is from a R/R CLL population, data from the "high-risk" sub-group in ALPINE could be used in a scenario analysis to estimate the effectiveness of zanubrutinib compared with ibrutinib in this subgroup. However, the EAG acknowledge that only a small proportion of participants in ALPINE reported have del17p or TP53 mutation and hence there is uncertainty associated with these estimates.
What is the expected effect on the cost-effectiveness estimates?	Subgroup analysis on clinical effectiveness data from SEQUOIA suggest that zanubrutinib is more effective in untreated "high-risk" CLL patients than in patients not considered to be "high-risk". Depending on the effectiveness of acalabrutinib in these subgroups, compared to the cost-effectiveness results in the overall untreated CLL population, zanubrutinib could be considered more cost-effective for "high-risk" patients and less cost-effective for non "high-risk" patients. The EAG cannot comment on whether zanubrutinib would no longer be considered cost-effective when compared with acalabrutinib in untreated CLL non "high-risk" patients. Due to the lack of available data comparing zanubrutinib with ibrutinib in untreated CLL and in the subgroup untreated "high-risk" CLL the EAG cannot comment on what effect this would have on the cost-effectiveness of zanubrutinib in this comparison. Based on the company's naïve comparison, which is subject to uncertainty, it is likely that zanubrutinib would still be considered cost-effective in this subpopulation. If the data from R/R "high-risk" CLL participants in the ALPINE trial were considered to be a suitable proxy for untreated "high-risk" CLL, it is likely that zanubrutinib could be considered more effective and hence cost-

Report section	4.3.3, 4.3.6.2.3, 6.2.6
	effective than ibrutinib in this subpopulation. However, the EAG do not consider the ALPINE data to be a suitable proxy and given the small proportion of participants being considered "high-risk" in ALPINE this bring further uncertainty to these estimates.
What additional evidence or analyses might help to resolve this key issue?	Data on the effectiveness of acalabrutinib disaggregated by risk status (with or without del17p or TP53 mutation) would improve the accuracy of the MAIC results. Moreover, a clinical trial(s) with head-to-head data comparing acalabrutinib versus zanubrutinib and ibrutinib versus zanubrutinib in an untreated CLL and the untreated "high-risk" CLL subpopulation would resolve this uncertainty.
Abbreviations: CLL = Chronic lymphocytic leukaemia; EAG = Evidence Assessment Group; MAIC = Matching-adjusted indirect comparison.	

1.6 Other key issues: summary of the EAG's view

None.

1.7 Summary of the EAG's view

The EAG base-case includes the EAG preferred assumption and was undertaken for both pairwise comparisons in previously untreated CLL and R/R CLL. Based on the deterministic results, zanubrutinib dominated both acalabrutinib and ibrutinib in untreated CLL as it was both less costly and more effective in terms of QALYs gained. The probabilistic EAG base-case analyses indicated zanubrutinib had an [redacted] probability of being cost-effective compared with acalabrutinib and ibrutinib at a willingness to pay threshold of £20,000 per QALY gained. Based on the deterministic results for the R/R CLL model, zanubrutinib dominated ibrutinib as it was both less costly and more effective. When compared with acalabrutinib, zanubrutinib was less costly and less effective; the ICER estimated for acalabrutinib was £340,019. The probabilistic EAG base-case analyses indicated zanubrutinib had an [redacted] probability of being cost-effective compared with acalabrutinib and ibrutinib at a willingness to pay threshold of £20,000 per QALY gained.

The most influential scenario analyses in the untreated CLL model comparing zanubrutinib with acalabrutinib were: 1) using alternative PFS and OS HRs; 2) using the utility values for PF and PD health states derived from the SEQUOIA trial; and 3) applying the utility decrement between PF and PD observed in the SEQUOIA trial to the company's preferred utility value for PF. In all these scenario analyses, zanubrutinib was less costly and less effective than acalabrutinib. However, the ICER estimated for acalabrutinib was in excess of £13 million for all scenarios.

The most influential scenario analyses in the untreated CLL model comparing zanubrutinib with ibrutinib were: 1) using the utility values for PF and PD health states derived from the SEQUOIA trial; 2) applying the utility decrement between PF and PD observed in the SEQUOIA trial to the company's preferred utility value for PF; and 3) applying alternative distributions for TTP and PrePS. In all these scenario analyses, zanubrutinib was less costly and more effective than ibrutinib and, hence, it was the dominant intervention.

The most influential scenario analyses in the R/R CLL model for both pairwise comparisons were: 1) using the utility values for PF and PD health states derived from the ALPINE trial; 2) applying the utility decrement between PF and PD observed in the ALPINE trial to the company's preferred utility value for PF; and 3) applying a Gompertz distribution to PFS. In all these scenario analyses,

zanubrutinib was the preferred treatment option. When compared with acalabrutinib, zanubrutinib was less costly and less effective. However, the ICER estimated for acalabrutinib was in excess of £250,000 for all scenarios. When compared with ibrutinib, zanubrutinib was less costly and more effective and, hence, it was considered the dominant intervention.

The cost-effectiveness results were robust across scenario analyses, in that zanubrutinib was the preferred treatment option in all scenarios. However, the EAG consider that the company's decision to undertake a CMA instead of a CUA was not the most suitable approach to address the decision problem in all comparators, except for ibrutinib in the R/R CLL population. The adoption of a CUA as the company's base-case may not have changed the conclusions but as a result of this assumption, there is uncertainty in some of the parameters included in the economic model, which the EAG tried to explore in scenario analysis. There are also uncertainties in the effectiveness data used in the economic models, mainly that the trial data used to inform the survival curves are immature. In addition, due to the lack of available data, the EAG have concerns about the use of data from patients with R/R CLL being used as a proxy in untreated "high-risk" CLL. In the R/R CLL model, the EAG do not agree with the company's decision to exclude VenR and, hence, data on the effectiveness and cost-effectiveness of VenR need to be included in this economic model. Finally, the EAG have identified potential issues with the SLR undertaken by the company and, hence, cannot be confident that all relevant clinical and HRQoL information was identified.

Tables 1.11, 1.12, 1.13. and 1.14 summarise the company's and EAG's base-case results.

Table 1.11: Summary of EAG's preferred assumptions and ICER – untreated CLL (zanubrutinib versus acalabrutinib)

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case CMA	[redacted]		
Mortality only from BTKi data (CMA)	[redacted]		
EAG's proposed CUA	[redacted]	[redacted]	Dominant
EAG's preferred base-case (CUA)	[redacted]	[redacted]	Dominant
EAG base-case probabilistic* (CUA)	[redacted]	[redacted]	Dominant
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALYs = Quality-adjusted life years.			

Table 1.12: Summary of EAG's preferred assumptions and ICER – untreated CLL (zanubrutinib versus ibrutinib)

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case CMA	[redacted]		
Mortality only from BTKi data (CMA)	[redacted]		
EAG's proposed CUA	[redacted]	[redacted]	Dominant
EAG's preferred base-case (CUA)	[redacted]	[redacted]	Dominant
EAG base-case probabilistic* (CUA)	[redacted]	[redacted]	Dominant
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALYs = Quality-adjusted life years.			

Table 1.13: Summary of EAG's preferred assumptions and ICER – R/R CLL (zanubrutinib versus acalabrutinib)

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case CMA	[redacted]		
EAG's preferred base-case (CUA)	[redacted]	[redacted]	£340,019*
EAG base-case probabilistic* (CUA)	[redacted]	[redacted]	£342,991*
*ICER is against acalabrutinib as it is more costly and more effective than zanubrutinib. Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALYs = Quality-adjusted life years.			

Table 1.14: Summary of EAG's preferred assumptions and ICER – R/R CLL (zanubrutinib versus ibrutinib)

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case CMA	[redacted]		
EAG's preferred base-case (CUA)	[redacted]	[redacted]	Dominant
EAG base-case probabilistic* (CUA)	[redacted]	[redacted]	Dominant
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALYs = Quality-adjusted life years.			

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Population	People with chronic lymphocytic leukaemia	As per scope	NA	The population is in line with the NICE scope.
Intervention	Zanubrutinib	As per scope	NA	The intervention is in line with the NICE scope.
Comparator(s)	For untreated CLL, including (but not limited to): • acalabrutinib (17p deletion or TP53 mutation or if fludarabine or bendamustine-based regimens are not suitable) • ibrutinib (17p deletion or TP53 mutation) • ibrutinib with venetoclax (subject to ongoing NICE appraisal) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab	Previously untreated adults with CLL who are unsuitable for FCR and BR therapy: • acalabrutinib Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable: • acalabrutinib • ibrutinib Adults with R/R CLL who have had at least one previous therapy: • acalabrutinib • ibrutinib	Previously untreated adults with CLL who are unsuitable for FCR and BR therapy: • FCR, BR: Not considered standard of care in this cohort by definition as patients are deemed unsuitable for therapy. Low usage confirmed by UK prescribing data with [redacted] of unfit (defined as patients aged >65 years or patient age ≤65 with comorbidities) patients receiving these therapies.[1] • Venetoclax-obinutuzumab: Low usage of venetoclax-obinutuzumab in this population as confirmed	The EAG has concerns that venetoclax-obinutuzumab and venetoclax-rituximab may have been omitted from the comparisons despite inclusion in the 2022 British Society for Haematology guidelines.[2] Additionally, BR is a comparison in the key trial of untreated CLL, SEQUOIA. Further comment is provided in Section 2.3.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	• fludarabine, cyclophosphamide and rituximab • venetoclax with obinutuzumab • venetoclax (17p deletion or TP53 mutation and if B-cell receptor pathway inhibitor is unsuitable) For relapsed or refractory CLL, including (but not limited to): • acalabrutinib • ibrutinib • venetoclax (if disease has progressed after a B-cell receptor pathway inhibitor) • venetoclax with rituximab • idelalisib with rituximab		by UK prescribing data which reported that [redacted] of unfit, previously untreated patients are treated with BTKis. In contrast, only [redacted] of unfit patients receive treatment with a venetoclax-based regimen.[1] Feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews and an advisory board (03 November 2022) conducted by the Company, supported that venetoclax-obinutuzumab usage in this population was low and it was typically used to treat more 'fit' patients who are younger and do not present with comorbidities given the risk of tumour lysis syndrome and GI side effects. These patients would typically be eligible for FCR and/or BR and as such, the	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			treatment is not relevant to this population. • Chlorambucil with or without rituximab or obinutuzumab: Chlorambucil-based CIT is no longer recommended since targeted pathway inhibitors have represented a paradigm shift in front-line treatment.[2] Low usage of chlorambucil-based CIT in this population as confirmed by UK prescribing data with only 4% of unfit patients receiving this therapy.[1] • Ibrutinib-venetoclax: Subject to an ongoing NICE appraisal (ID3860) and is neither routinely commissioned by NHS England, nor does it reflect established NHS clinical practice. Previously untreated adults with CLL who have a 17p	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable: • Venetoclax-obinutuzumab: 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. Low usage of venetoclax-obinutuzumab in this population as confirmed by UK prescribing data, with [redacted] of untreated patients with a 17p deletion or TP53 mutation being treated with a BTKi and [redacted] receiving treatment with venetoclax-obiutuzumab.[1] • Furthermore, feedback received from five UK clinicians, gathered in double-blinded, 1:1	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			interviews and an advisory board (03 November 2022) conducted by the Company, supported that venetoclax-obinutuzumab usage in this population was low and it was typically used to treat more 'fit' patients who are younger and do not present with comorbidities given the risk of tumour lysis syndrome and GI side effects. These patients would typically be eligible for FCR and/or BR and as such, the treatment is not relevant to this population. • Idelalisib-rituximab, venetoclax monotherapy: Only recommended for relapsed patients who are unsuitable for or who are refractory to a BTKi-based treatment, i.e., in patients not eligible for treatment with zanubrutinib with	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			low usage in this population as supported by UK prescribing data ([redacted]). Adults with R/R CLL who have had at least one previous therapy: • Venetoclax-rituximab: Treatment 'sequencing' suggests that the optimal treatment following progression varies depending on the front-line therapy – 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. Whilst venetoclax-rituximab is recommended by NICE for treating R/R CLL, it is primarily used in	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			patients previously treated with a BTKi.[3] • Patients eligible for zanubrutinib are those who have not previously received treatment with a BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial[4]), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib. • Venetoclax monotherapy: 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 del17p or TP53 mutation whose disease has progressed after both CIT and a B-cell receptor pathway inhibitor, i.e., in patients not eligible for	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			treatment with zanubrutinib. • Idelalisib-rituximab: Only recommended for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment, i.e., in patients not eligible for treatment with zanubrutinib.	
Outcomes	• overall survival • progression-free survival • response rate • time-to-treatment failure • adverse effects of treatment • health-related quality of life	As per scope	NA	The outcomes are mainly in line with the NICE scope. However, time to treatment failure was not included as an outcome in the SEQUOIA trial. Further comment is provided in Section 2.4.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal	Cost-effectiveness of zanubrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR therapy: Cost-minimisation analysis of zanubrutinib vs. acalabrutinib. Cost-effectiveness of zanubrutinib in previously untreated adults with CLL who	NA	Cost-effectiveness of zanubrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR: Due to the lack of evidence available for patients with del17p independent from patients without del17p in the acalabrutinib arm, a MAIC is presented for the overall untreated CLL population. The MAIC results presented by the company report large

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	have a 17p deletion or TP53 mutation and in whom CIT is unsuitable: Cost-minimisation analysis of zanubrutinib vs. acalabrutinib and ibrutinib. Cost-effectiveness of zanubrutinib in adults with R/R CLL who have had at least one previous therapy: Cost-minimisation analysis of zanubrutinib vs. acalabrutinib and ibrutinib.		uncertainties in the estimates and do not produce conclusive evidence of non-inferiority for zanubrutinib against acalabrutinib. The EAG considers that this undermines the justification to present a CMA as the base-case analysis, while further uncertainty remains on the efficacy of zanubrutinib in patients with del17p or TP53 versus without. The evidence for zanubrutinib versus ibrutinib in untreated CLL patients with del17p used R/R patient data as a proxy; based on clinical advice, this approach was not considered appropriate by the EAG, as R/R is not a suitable proxy for "high-risk" (i.e. del17p or TP53 mutation). Furthermore, in the company's naïve comparison using data from Mato *et al*., (2018) non-inferiority was not demonstrated for PFS (HR: [redacted]; 95% CI, [redacted], [redacted]) however there was a statistically significant difference in OS demonstrated between zanubrutinib compared with ibrutinib (HR: [redacted]; 95% CI, [redacted], [redacted]).[5] Cost-effectiveness of zanubrutinib in adults with R/R CLL who have had at least one previous therapy: A CMA approach comparing zanubrutinib versus ibrutinib is potentially a

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
				conservative scenario considering the evidence submitted. The results generated by the multiple MAICs between zanubrutinib and acalabrutinib do not provide conclusive evidence of non-inferiority on key outcomes but suggest a high degree of uncertainty, which undermines the justification for a CMA in this comparator.
Special considerations including issues related to equity or equality	If the evidence allows the following subgroups will be considered: Untreated CLL Relapsed or refractory CLL Within untreated CLL, if the evidence allows the following subgroups may be considered: People for whom fludarabine-based therapy is suitable People for whom fludarabine-based therapy is unsuitable People for whom fludarabine-based and bendamustine-based therapy are unsuitable People with a 17p deletion or TP53 mutation	The following subgroups will be considered: Untreated CLL Relapsed or refractory CLL Within untreated CLL, the following subgroups of patients are considered appropriate: People for whom fludarabine-based and bendamustine-based therapy are unsuitable People with a 17p deletion or TP53 mutation	Assessments in the following subpopulations of patients with untreated CLL are omitted given the lack of clinical trial evidence available for zanubrutinib in this population: People for whom fludarabine-based therapy and/or bendamustine-based therapy is suitable	The EAG considers that the categorisation of participants in Cohort 1 of the SEQUOIA study may be considered "fit" rather than "unfit," as they were eligible for BR (see Section 2.5). This may have implications for the economic model of untreated CLL (see Section 4.3.3).

Source: CS, Table 2[6]

Abbreviations: BR = bendamustine-rituximab; BSH = British Society for Haematology; BTKi = Bruton tyrosine kinase inhibitor; CDF = Cancer Drug Fund; CIT = chemo-immunotherapy; CLL = chronic lymphocytic leukaemia; CMA = cost minimisation analysis; del17p = 17p deletion; FCR = fludarabine, cyclophosphamide and rituximab; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; R/R = relapsed/refractory.

2.1 Population

In the SEQUOIA trial of untreated chronic lymphocytic leukaemia (CLL), participants were patients with a diagnosis of CD20-positive (CLL) or small lymphocytic leukaemia (SLL) that met International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria[7] and had no prior treatment (CS, Table 9).[6] Participants could be aged ≥ 65, or aged 19 to 64 with either: a creatinine clearance < 70 mL/min; history of serious infection or multiple infections in the past two years; and/or a cumulative illness rating scale (CIRS) score > 6 (CS, Table 9).[6]

In the ALPINE trial of relapsed or refractory (R/R) CLL, participants were people aged ≥ 18 years with a diagnosis of CLL or SLL that met the iwCLL criteria,[7] R/R to at least one prior systemic therapy for CLL or SLL (CS, Table 9).[6]

EAG Comment: The populations of SEQUOIA and ALPINE are in line with the NICE decision problem.

The design of SEQUOIA was split into four cohorts: Cohort 1, Cohort 1a, Cohort 2 and Cohort 3. Cohort 1a was not considered by the company to be applicable to the submission because it only included participants recruited in China (CS Section B.2a.3.1, p.40).[6] The EAG's clinical advisor agreed with this assumption. In Cohort 3 of SEQUOIA, participants received zanubrutinib in combination with venetoclax, though the company noted that this Cohort was not deemed relevant to the decision problem, hence this Cohort was not included in the CS (CS Section B.2a.3.1, p.40).[6] The EAG agrees with the company that the intervention in Cohort 3 of SEQUOIA is not relevant to the CS and their decision to not include this Cohort in the CS.

2.2 Intervention

In both the SEQUOIA trial in untreated CLL and the ALPINE trial in R/R CLL, the intervention was 160 mg oral zanubrutinib (administered as two 80 mg capsules) twice daily until unacceptable toxicity or disease progression (CS, Table 10 and Table 29).[6]

EAG Comment: The interventions in SEQUOIA and ALPINE are in line with the NICE decision problem.

2.3 Comparators

The company considered the following comparators within the CS.

- Previously untreated adults with CLL unsuitable for fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine-rituximab (BR) therapy: acalabrutinib
- Previously untreated adults with CLL who have a 17p deletion (del17p) or TP53 mutation and in whom chemoimmunotherapy (CIT) is unsuitable: acalabrutinib, ibrutinib
- Adults with R/R CLL who have had at least one previous therapy: acalabrutinib, ibrutinib

The company provided rationales for their decisions in the decision problem table (CS, Table 2),[6] and in another table, replicated in Table 2.2 (CS, Table 1).[6]

Table 2.2: Comparators considered by the company to be relevant to the appraisal

Comparator listed in the final scope	Relevance to this appraisal	Rationale
Previously untreated adults with CLL who are unsuitable for FCR and BR therapy		
Acalabrutinib	✓	Key comparator

Comparator listed in the final scope	Relevance to this appraisal	Rationale
Venetoclax with obinutuzumab	×	An alternative treatment option to BTKis, low usage in the "unfit" population and typically used to treat more 'fit' patients as supported by UK prescribing data and UK clinical expert feedback[1,8]
Chlorambucil with or without rituximab	×	No longer recommended as per 2022 BSH CLL guidelines[2] and low usage confirmed by UK prescribing data
Obinutuzumab with chlorambucil	×	
BR	×	Patients are ineligible for BR in this population by definition
FCR	×	Patients are ineligible for FCR in this population by definition
Ibrutinib with venetoclax	×	Not approved by NICE
Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable		
Acalabrutinib	✓	Key comparator
Ibrutinib	✓	Key comparator
Venetoclax with obinutuzumab	×	Low usage in population; typically used in fitter patients; usage unlikely to change with introduction of zanubrutinib, as supported by UK prescribing data and UK clinical expert feedback[1,8]
Venetoclax monotherapy	×	Not recommended in patients who have not previously received treatment with a BTKi patients, which is the population eligible for zanubrutinib
Idelalisib with rituximab	×	
Adults with R/R CLL who have had at least one previous therapy		
Acalabrutinib	✓	Key comparator
Ibrutinib	✓	Key comparator
Venetoclax with rituximab	×	Not recommended in patients who have not previously received treatment with a BTKi, which is the population eligible for zanubrutinib
Venetoclax	×	
Idelalisib with rituximab	×	

Source: CS Table 1[6]
Key: ✓= relevant to appraisal; × = not relevant to appraisal
Abbreviations: BR = Bendamustine-rituximab; BSH = British Society for Haematology; BTKi = Bruton tyrosine kinase inhibitor; CLL = Chronic lymphocytic leukaemia; CS = Company submission; FCR = Fludarabine, cyclophosphamide and rituximab; NICE = National Institute for Health and Care Excellence; R/R = Relapsed/refractory.

In the CS, Cohort 1 of the SEQUOIA trial compared zanubrutinib with BR in untreated CLL participants, while ALPINE compared zanubrutinib with ibrutinib in participants with R/R CLL (CS, Table 9).[6]

EAG comment: Clinical advice to the EAG highlighted that BR is no longer recommended for frontline use in people with untreated CLL in the UK. According to the British Society for Haematology (BSH)

guidelines on CLL,[2] bendamustine-based CIT, including BR, is also no longer recommended as a first-line treatment option. The EAG appreciates that the BSH guidance has only recently been amended,[2] while the EAG's clinical advisor noted that the comparison with BR was not unreasonable. However, the EAG believes there may be some uncertainty surrounding Cohort 1 of SEQUOIA to future NHS practice.

Clinical advice to the EAG also disagreed with the exclusion of venetoclax with rituximab (VenR). They disagreed with the company's perspective that VenR, would not be recommended in patients who have not previously received treatment with a Bruton tyrosine kinase inhibitor (BTKi), as there will be some patients who have had CIT for whom a BTKi would be a second-line option. For the relapsed population, the BSH guidelines recommend that venetoclax with or without rituximab as one of the treatments of choice.[2] Therefore, the EAG cannot be certain that potentially relevant trial evidence comparing zanubrutinib with VenR has been omitted from the submission; this is especially pertinent for the matching-adjusted treatment comparison (MAIC). Data were available to conduct unanchored MAICs comparing zanubrutinib with VenR.[9] However, the company did not include VenR as a comparator in the decision problem despite being included in the NICE scope.

The EAG disagree with the exclusion of venetoclax-obinutuzumab (VenO) as a relevant comparator to zanubrutinib in the untreated CLL population. NICE guidance on the use of VenO (TA663) states that VenO is a recommended as an option for untreated CLL if: 1) patients are "high-risk" (i.e. del17p or TP53 mutation is present); and 2) patients are not "high-risk" and FCR or BR is unsuitable.[10] This is the population the company specify in the untreated CLL economic model.[6] The EAG's clinical advisor agreed that VenO would be an option for untreated CLL and disagreed with the CS that usage was low in the UK. Additionally, based on advice to the EAG from the clinical expert, the EAG determined that the evidence used to support the use of VenO in "fit" untreated CLL was based on data in "unfit" CLL patients. The EAG acknowledges that NICE guidance states that VenO could be used in "fit" patients (i.e. not "high-risk" and where FCR or BR is suitable) but note this guidance was informed based on the CLL14 trial, which was undertaken in patients with untreated CLL who would be considered "unfit" because they were older and had a CIRS score > 6.[11] Data were available to conduct unanchored MAICs comparing zanubrutinib with VenO. However, the company did not include VenO as a comparator in the decision problem despite being included in the NICE scope.[11]

2.4 Outcomes

Both SEQUOIA and ALPINE assessed most of the outcomes outlined in the decision problem: overall survival (OS), progression-free survival (PFS), adverse events (AEs) and health-related quality of life (HRQoL) (CS, Table 9).[6] Response rate was measured as overall response rate (ORR) in both SEQUOIA and ALPINE (CS, Table 9).[6] However, while ALPINE measured time to treatment failure (TTTF), correspondence with the company via the points for clarification letter established that TTTF data were not available for SEQUOIA.[12] Other outcomes assessed in both SEQUOIA and ALPINE not relevant to the decision problem were pharmacokinetics, duration of response (DOR) and medical resource utilisation (CS, Table 9).[6]

EAG Comment: Both SEQUOIA and ALPINE planned to assess the key outcomes outlined in the final NICE scope. However, CS Table 9 (CS Section B.2.2, p. 39) outlines that, while PFS, AEs and HRQoL were used in the economic models for both untreated and R/R CLL, OS was only considered in the economic model for R/R CLL.[6] This issue is further discussed in Section 3.2.1. Additionally, the company's response to the clarification letter established that the inclusion of TTTF as an endpoint in SEQUOIA was a typographical error in the CS and that data were not available for TTTF for this trial.[12] This means the outcomes in SEQUOIA do not fully align with the NICE decision problem.

2.5 Other relevant factors

The Committee for Medicinal Products for Human Use (CHMP) authorised the use of zanubrutinib for use as a monotherapy for the treatment of adults patients with CLL on 13 October 2022 (CS, Table 3).[6] Subsequently, the European Medicines Agency (EMA) granted marketing authorisation for the use of zanubrutinib on 17 November 2022, followed by approval by the Medicines and Healthcare products Regulatory Agency (MHRA) through the European Commission Decision Reliance Procedure on 6 January 2023 (CS, Table 3).[6]

The patient submissions received as part of the CS from CLL Support, Leukaemia Care and Lymphoma Action highlighted the need for further treatment options in the "fit" population.[13-15] The company state that, due to the lack of clinical trial data available for "fit" patients (i.e. those with untreated CLL for which FCR or BR is suitable), they did not present an assessment of this population (CS Section B.1.4, p.35).[6] The company highlight that this may pose an equality issue in that zanubrutinib may not be prescribed to younger and fitter patients with untreated CLL (CS Section B.1.4, p.35).[6]

EAG Comment: The EAG has concerns surrounding the categorisation of participants in the SEQUOIA trial as "unfit." The company's definition of "unfit" is that participants would be unsuitable for treatment with FCR and BR, based on their placement of zanubrutinib in the clinical pathway (CS, Figure 1).[6] However, participants in SEQUOIA Cohort 1 were randomised to either zanubrutinib or BR but were ineligible for FCR (CS, Table 9).[6] By the company's definition, this means the population in SEQUOIA Cohort 1 are deemed to be "fit." Additionally, the BSH guidelines state that CIT would only be considered in "fit" patients with intact TP53;[2] participants in SEQUOIA Cohort 1 were eligible for CIT as they could receive BR (CS, Table 10).[6] However, the EAG acknowledges that patients randomised to the SEQUOIA trial were older (65 years and over), but if they were 18-64 years, they had to have a creatinine clearance below 70 mL/min, history of previous serious infection or multiple infections in the past 2 years and/or a Cumulative Illness Rating Scale (CIRS) score > 6,[6] and, while they were eligible for BR, they were not considered "fit" for intensive CIT. The EAG appreciate that the definition of "fitness" is non-binary and that, while BR is considered CIT, according to the BSH guidelines it is considered an acceptable alternative for "fit" patients for whom FCR is contraindicated. As such, participants in SEQUOIA Cohort 1 can be considered "fit" as per BSH guidelines. This has implications for the economic model of untreated CLL, which assumed that the SEQUOIA trial data were an adequate proxy for the "unfit" population. This issue is discussed further in Section 4.3.3.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company undertook one integrated systematic literature review (SLR) to identify existing clinical studies in CLL. Zanubrutinib was assessed as a monotherapy for adult patients with either previously untreated or R/R CLL and was to be compared with several comparators (see Section 3.1.2). The methodology of the integrated SLR and the search results for the clinical studies search were outlined in CS Appendix D.[16]

3.1.1 Searches

The search strategy consisted of concepts from the population combined with interventions outlined in the NICE scope and several search filters for the inclusion of certain study types and exclusion of animal studies and other study types.[17]

The company conducted the original clinical effectiveness searches on 01 July 2022; no further update searches have been reported. The company searched for randomised controlled trials (RCTs) and observational studies in a range of electronic bibliographic databases, including Embase, Embase Classic and MEDLINE via Embase.com, as well as Cochrane databases CENTRAL and Cochrane Clinical Answers via the Cochrane Library website. The company provided a single search strategy in CS Appendix D Table 1 for the searches they undertook in Embase.com and in Table 2 for the Cochrane Library search.[16] The company used two search filters for study design: one for RCTs and one for observational studies. Relevant conferences were identified and listed by the company as being sought through the reported searches performed in Embase via Embase.com (CS Appendix D, Table 1).[16] The company provided a rationale for the time limits imposed to the searches, which were limited to publication date between 01 January 2007 and 01 July 2022. English language limits were imposed but no rationale was provided.

A separate grey literature search on the NICE and Scottish Medicine Consortium (SMC) websites was conducted on 11 August 2022 and reported in CS Appendix D (Table 6).[16] This search was limited to "2 years" up to the search date.

A summary of the CS search-related information is provided in Table 3.1.

Table 3.1: Summary of searches conducted by the company for clinical effectiveness studies

Resource category	Resource	Host source	Date Range	Date search	Search strategy terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	Embase	Embase interface	2007-01.07.2022	01.07.2022	Partially	Yes	Yes
	MEDLINE						
	Embase Classic						
	CENTRAL	Cochrane Library interface			Yes	Yes	Yes
	Cochrane Clinical Answers				No	No	No
	ISPOR			01.07.2022	NA	NR	Yes[d]

Conference abstracts[b]	ASCO	Embase interface	2007-01.07.2022				
	ESMO						
	ASH						
	ICML						
	EHA						
Grey literature	NICE.org.uk	NR	2 years[c]	11.08.2022	Yes	Yes	Yes
	scottishmedicines.org.uk						

Source: Based on CS, Appendix D[16]

[a] The company provided a single SLR covering Embase, MEDLINE and Embase Classic. The EAG requested in the clarification letter individual search strategies including the following information: URL and platform of the database used, name of the database (with time coverage), date when the search was run, and number of retrieved records per database. As the Company failed to provide this information, the search strategy terms and the number of hits per line for each resource can not be verified by the EAG.

[b] The company reports the conference abstracts were obtained from Embase

[c] No precise dates given for the start of the search date range, the search string shows limitation applied for 2 years (CS, Appendix D, Table 6)[16]

[d] Results embedded in PRISMA Embase results

Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Haematology; CENTRAL = Cochrane Central Register of Controlled Trials; CS = Company submission; EHA = European Haematology Association; ESMO = European Society for Medical Oncology; ICML = International Conference on Malignant Lymphoma; ISPOR = The Professional Society for Health Economics and Outcomes Research; N = Number; NA = Not applicable; NICE = National Institute for Health and Care Excellence; NR = Not reported.

EAG comment: The EAG appraised the searches presented in the CS using the Peer Review of Electronic Search Strategies (PRESS) checklist and the latest NICE methods manual.[18,19]

According to the reported search strategies, the EAG is uncertain whether all relevant studies have been identified. The EAG requested the company to submit individual search strategies for each of the databases searched (e.g. Embase, MEDLINE, Embase Classic, Cochrane CENTRAL and Cochrane Clinical Answers), providing additional search information such as the name and date coverage of the databases at the time of searching, the date in which the search was run, and the number of hits per line. This standard of reporting and recording searches separately is established as good practice in systematic reviews methodology.[20,21] In their response, the company noted only one search needed to be performed within the Embase interface and all necessary information had been provided.[12] Since the company did not conduct separate searches for Embase, MEDLINE, Embase Classic databases, the EAG was not able to quality check individual strategies against the databases reported.[12] The EAG would like to acknowledge that the use of Embase.com to interrogate MEDLINE and Embase databases is not a standard and that there are other database platform providers such as OVID that allow access to such databases. The EAG does not have access to Embase.com because it is not freely available hence why the EAG requested individual search strategies for each database. Given that the EAG are unable to assess the quality of the search strategy used by the company the EAG are unable to verify that all relevant studies were identified across the different databases from this one search. The following comments from the EAG, which are based on best practice guidelines, are relating to the search process undertaken and the assumptions made as part of that search.

The EAG notes that one of the databases used, 'Embase Classic' is a back file covering citations between 1947 and 1973; the company confirmed this within the clarification letter response,[12] which

leads the EAG to question the relevancy of this source to the decision problem, as the company imposed publication date limits between 2007-2022 for which they provide a rationale in CS Appendix D.[16] The EAG is unable to comment on the efficiency of Embase.com to retrieve MEDLINE records, since they are not re-indexed with the corresponding Emtree controlled vocabulary terms but "mapped."[22]The EAG notes that the approach to identifying evidence on the range of interventions included did not maximise sensitivity, as additional alternative drug names/codes could have been used that would have impacted on the number of records retrieved. Furthermore, the search strategy reported in CS Appendix D (Table 2) presents the combined search strategy for CENTRAL and Cochrane Clinical Answers databases.[16] On assessment, the presented strategy does not suggest that records from the latter database would have been retrieved, as line 3 in Table 2 limits the search results to trials only (CS, Appendix D).[16] This means that only CENTRAL records would have been retrieved and downloaded for further assessment. Since the company did not provide individual search strategies for CENTRAL and Cochrane Clinical Answers database on request, the EAG can only assume that records from the Clinical Answers database were not included in the review and that the PRISMA flow chart for the selection of clinical studies included in CS Appendix D incorrectly reports this study identification and selection process.[16]

The reported date of searching being at least nine months ago raises concerns surrounding the currency of the evidence included in the submission. The EAG acknowledge that this may be a common concern of the HTA process and its variable timelines. Furthermore, the grey literature searches were very limited in time and approach, which may have led to potential publication and outcome reporting bias.

The company provided no supporting information on the rationale for the selection and use of the filters for study design (e.g. RCTs), as well as their origin and filter performance (sensitivity, specificity and recall), as would be considered good practice. The EAG raised this issue in the clarification letter and the company responded that the origin of the RCT and observational study filters came from the Scottish Intercollegiate Guidelines Network (SIGN).[12] On closer inspection, the EAG identified that the original SIGN RCT study type filter would have excluded conference abstracts and conference proceedings as these type of studies are excluded in the original RCT filter designed by SIGN. In order to avoid the exclusion of these publication types, the company cut out the two lines from the RCT filter which referred to conference abstracts and proceedings. This manipulation would have resulted in conference abstracts and proceedings being present in the final set of results once the filter was combined with the PICOs elements of the search. The EAG would like to note that the company did not provide a rationale for this filter alteration, nor did they report this alteration in the search methods. The EAG understands that these two lines had been removed from the filter to **not exclude** conference abstracts from the search (as the original filter excludes this type of studies). However, the EAG is unable to ascertain whether this alteration of a pre-tested study type filter would have implications in the filter performance. Furthermore, SIGN states that their RCT filter is less sensitive than other validated filters, such as the Cochrane RCT sensitivity-maximising filter, which would have an impact on the retrieval of RCTs.[23]

The company did not provide separate full search strategies for each of the databases searched to locate conference papers and/or conference meeting webpages and, as such, the EAG is unable to comment on the ability of the reported searches to retrieve relevant, up-to-date conference abstracts. The EAG raised this issue in the clarification letter but the company provided no further additional conference searches, instead stating that: "the grey literature search covered all recent conferences from international meetings considered potentially relevant to the treatment of chronic lymphocytic leukaemia (CLL)"(A3, page 4).[12] The company failed to provide details of what "recent" meant in the context of these searches and whether they visited each individual conference site to search for potentially relevant abstracts, or they relied on the Embase.com search to locate conference abstracts,

or reasoning for conducting searches for conferences within Embase.com.[12] The latest edition of the Cochrane Handbook states that: "Conference abstracts can be a rich source of RCT evidence. Within Embase, these records have been indexed using automated indexing procedures, and in most cases the index terms applied automatically are about subject topics or content rather than study type."[24] This means that if a conference paper was indexed in Embase based on its topic-specific index terms (e.g., CLL) but did not include any RCT-specific index term, this paper would have been automatically excluded from the final set of results as per the company's search approach. Therefore, the EAG remains unclear as whether the reported search strategy would have identified all relevant conference papers from the conferences the company considered and listed as useful. Moreover, the EAG has concerns that the reported method for identifying relevant conference abstracts has not been robust enough and considers that, alongside the use of specific search approaches for Embase,[25] manual hand searching of relevant conference sites should have been performed and reported as per the PRISMA standards recommend.[21,26]

Furthermore, the EAG considers that using only one search term, "CLL," in non-bibliographic databases where no indexing or controlled vocabulary mapping of free-text terms occurs, such as the NICE and SMC websites, limits the ability of a search to retrieve all relevant records and that alternative spelling and search terms should have been considered. The EAG is therefore uncertain whether the reported grey literature searches would have retrieved all relevant unpublished reports. The EAG asked the company to clarify their approach to grey literature searching, to which the company responded with a rationale for the two-year limit as "standard practice" and a rationale for the selection of only two HTA bodies as "the only [ones] relevant to the UK"; no evidence or citations were provided by the company supporting this claim.[12] Grey literature searching aims to avoid publication and outcome reporting bias by identifying evidence from unpublished studies and unpublished data; there is no evidence that suggests a short time search period is adequate or recommended unless it is justified.[27] Furthermore, the NICE Health Technology Evaluations manual (PMG36) recommends that, for a NICE technology appraisal, evidence from non-UK sources should be sought.[19]

Concerns surrounding a single literature search encompassing different databases, potential alterations of validated study design filters, limited search criteria for the intervention and non-standard conference searching means the EAG have concerns about whether the SLR was sensitive enough to capture all available literature on the effectiveness of interventions in CLL.

3.1.2 Inclusion criteria

The company presented the eligibility criteria as summarised in Table 3.2 (CS, Appendix D).[16] Two reviewers independently screened studies at both title and abstract and full text stages, with arbitration from a third reviewer following any unresolved discrepancies regarding screening decisions (CS, Appendix D).[16]

Table 3.2: Eligibility criteria used in search strategy for RCT evidence

	Description	EAG comment
Inclusion criteria		
Population	Patients with chronic lymphocytic leukaemia	As per the NICE scope.

	Description	EAG comment
Interventions/ comparators	Brukinsa® (zanubrutinib) Imbruvica® (ibrutinib) Calquence® (acalabrutinib) Levact® (bendamustine) Vencylxto® (venetoclax) Mabthera®(rituximab) Fludara® (fludarabine) Cytoxan® (cyclophosphamide) Zydelig® (idelalsib) Gazyvaro® (obinutuzumab) Leukeran® (chlorambucil)	In the absence of head-to-head trial evidence of zanubrutinib versus all UK relevant comparators, an indirect treatment comparison was undertaken.
Outcomes	Efficacy (e.g., PFS, ORR, OS, DOR, TTF, HRQoL, TTP, TTD, PPS, TTTD) Safety (e.g., adverse events)	The outcomes in the NICE scope are included.
Study design	RCTs Non-RCTs Observational studies (including patient registries)	RCTs represent the gold standard for assessing intervention effectiveness and the main evidence is based on this study design.[28]
Language restrictions	English	Restricted to English language, so prone to potential language bias.[20]
Exclusion criteria		
Population	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest	The company informed the EAG that these studies would not be representative of the target population.[12] This was confirmed by the EAG's clinical advisor. The company provided an adequate response to the EAG's request to define "a minority of patients being of interest" in the clarification letter.[12] The company explained that studies reporting a mixed population (i.e. populations covering CLL and other conditions) were excluded from the SLR if results were not reported specifically by disease type, or if patients with CLL comprised only a minority of the population (defined as < 50% of the total population). Results from mixed populations containing only a minority of patients with CLL would be heavily confounded by results from the other disease populations; generalising the results to CLL would introduce substantial uncertainty.

	Description	EAG comment
Interventions	No intervention / comparators of interest	The EAG have no concerns with this decision.
Outcomes	No reported outcomes of interest, i.e. only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes	The EAG have no concerns with this decision.
Study design	Cross-sectional studies Animal studies In vitro/ex vivo studies Individual case study reports	These studies do not include a comparison group, so it is not possible to compare the effects of the intervention with alternative treatments or best supportive care. Therefore, the EAG have no concerns about their exclusion.
Language restrictions	Non-English	The EAG assumed the exclusion of studies not reported in English was due to pragmatic reasons. However, this may be a cause of selection bias in identifying relevant treatments in the network.

Source: CS Appendix D, Table 7[16]
Abbreviations: DOR = Duration of response; EAG = Evidence Assessment Group; HRQoL= Health-related quality of life; NA = Not applicable; ORR = Overall response rate; OS = Overall survival; PfC = Points for clarification; PFS = Progression-free survival; PPS = Post-progression survival; RCT = Randomised controlled trial; SLR = Systematic literature review; TTD = Time-to-death; TTF = Time-to-treatment failure; TTP = Time-to-progression; TTTD = Time-to-treatment-discontinuation; UK = United Kingdom.

EAG Comment: The SLR conducted was broader than the scope of the CS and, as such, the company only extracted studies if they included zanubrutinib, acalabrutinib or ibrutinib as the treatments of interest.[6] The comparators included in the SLR were relevant to the NICE scope,[17] with the focus being on comparisons involving zanubrutinib, acalabrutinib and ibrutinib.[16]

The company restricted the SLR to studies reported in English, which may present a bias.[20] The EAG is unable to assess the possible effect of excluding non-English studies on the SLR results.

3.1.3 Data extraction

The company described their methods for data extraction as follows: "data were extracted by a single reviewer, followed by a quality check by a second independent reviewer" (CS Appendix D, Section D.1.3.3, p.12).[16]

EAG comment: The criteria used for data extraction were narrower compared to the study selection criteria. As alluded to in Sections 2.3 and 3.1.2, the EAG have concerns surrounding the exclusion of VenR and VenO as relevant comparators within the CS (see Section 1.1.1).

The EAG disagree with the exclusion of extracted data on VenR from the SLR results within the submission, for reasons outlined in Section 2.3. As also documented in Section 2.3, VenO is a recommended option for initial therapy in patients unsuitable for CIT and, thus, it is not possible from the company analyses to assess the effectiveness of zanubrutinib compared with these interventions as data were not extracted. The EAG explored this uncertainty in Section 3.5.

The company's method represents a pragmatic approach to data extraction where staff resources are limited, though does not represent best practice, where two people independently extract data.[20] Furthermore, the company do not state how the "quality check by a second independent reviewer" was conducted.

It is unclear whether the company approached individual study authors for missing data or to clarify information. This may impact on the SLR and the results of the MAIC, as missing data has a significant influence on the choice of prognostic variables in the model being traded off with the effective sample size (ESS). Minimising missing data for both outcomes and prognostic variables raises the overall quality of analyses.

3.1.4 Quality assessment

The company describe their process for assessing risk of bias in CS Appendix D.[16] Quality assessment was undertaken using a checklist from the "NICE guidelines manual."[19] The risk of bias results in each domain and overall were presented for each study in CS Appendix D (Table 19),[16] CS Section B.2a.5 (p.57-8),[6] and CS Section B.2b.5 (p.84-5).[6]

EAG Comment: The process for undertaking quality assessment was not reported in the CS.[16] As such, the EAG cannot comment on the appropriateness of the methods used to appraise study quality in the SLR.

The quality assessments for SEQUOIA and ALPINE are critiqued by the EAG in Sections 3.2.1.1 and 3.2.2.1 respectively. The quality assessments for the other trials forming part of the CS evidence synthesis lacked detail in supporting statements for individual domain assessments. The company only provided additional supporting evidence to their risk of bias judgements in the trials that included zanubrutinib.[12,16] Therefore, the EAG could not comment on the risk of bias in trials included in the SLR, though do note a lack of confirmation of allocation concealment in all trials and increased risk of detection and performance biases, particularly for subjective outcomes, due to a lack of blinding of participants and health care providers.[20] The overall risk of bias profiles suggest that all trials included in the SLR were prone to bias.

The company did not report any sensitivity analyses excluding studies in the SLR based on study quality and risk of bias profiles. This was presumably due to only one RCT involving zanubrutinib being identified in both the untreated and R/R CLL populations.

3.1.5 Evidence synthesis

The SLR included eight RCTs for zanubrutinib, ibrutinib and acalabrutinib in the treatment of patients with CLL: SEQUOIA;[29] ALPINE;[30] RESONATE-2;[31] ALLIANCE;[32] RESONATE;[33]; ELEVATE-TN;[34] ASCEND;[35] and ELEVATE-RR.[36] The SEQUOIA and ALPINE trials were used as the pivotal trials on which evidence was informed.[29,30] SEQUOIA was conducted in participants with untreated CLL,[29] while ALPINE was conducted in participants with R/R CLL.[30] Full details are provided in CS Appendix D, Section D2.[16]

In patients with previously untreated CLL, the company conducted a MAIC to assess the comparative effectiveness of zanubrutinib versus acalabrutinib in the absence of head-to-head data. The MAIC utilised individual patient-level data (IPD) from SEQUOIA,[29] as well as published cohort data from ELEVATE-TN.[34] Full details of the MAIC in the untreated population are given in Section 3.3.1. In patients with R/R CLL, the company reported two MAICs to compare zanubrutinib with acalabrutinib in the absence of head-to-head data. The MAICs utilised IPD from ALPINE,[30] as well as published

cohort data from ELEVATE-RR and ASCEND.[35,36] Full details of the MAICs in the R/R CLL population are provided in Section 3.3.2.

EAG Comment: The eight identified studies in the SLR provide indirect evidence to inform the decision problem. However, the EAG has concerns that, for the reasons stated in Sections 3.1.1 and 3.1.3, this could potentially be an incomplete and selective set of trials.[20]

Due to the paucity of evidence of any comparison involving treatments in the network including zanubrutinib, the EAG requested further justification from the company as to why data were not extracted from RESONATE.[33] In response, the company justified their approach as following NICE methods, whereby an indirect treatment comparison (ITC) using RESONATE was not considered necessary in the assessment of zanubrutinib versus ibrutinib in patients with R/R CLL.[12] Given the paucity of evidence for trials involving zanubrutinib, there was the potential to extend the analysis reported in the CS by including the data from RESONATE. However, in general the EAG considers the response by the company adequate.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company identified one study assessing the effectiveness of zanubrutinib in people with untreated CLL, SEQUOIA,[29,37] and a second study assessing the effectiveness of zanubrutinib in people with R/R CLL, ALPINE.[6,30,38] SEQUOIA is discussed in Section 3.2.1 and ALPINE is discussed in Section 3.2.2.

3.2.1 SEQUOIA trial

3.2.1.1 SEQUOIA trial design and quality assessment

The evidence of the effectiveness of zanubrutinib in patients with untreated CLL came from the SEQUOIA trial (NCT03336333).[6,29,37] SEQUOIA is a phase 3, open-label, multicentre study across 14 countries, with a total of 64 participants recruited from UK sites (number updated in the company's response to the clarification letter).[12] SEQUOIA planned to report on OS, PFS, ORR, AEs and HRQoL, with PFS, AEs and HRQoL used in the economic model (Sections 4.3.6 to 4.3.8 of EAG report). As previously described in Section 2.4, it was established in the response to the clarification letter that TTTF, a key outcome in the NICE decision problem, was not measured in SEQUOIA.[12] A summary of the trial methodology is shown in Table 3.3.

Table 3.3: SEQUOIA study design

Category of design	Details
Trial design	Phase 3, open-label, randomised, multicentre.
Population	People with a diagnosis of CD20-positive CLL or SLL that met iwCLL criteria; no prior treatment; aged ≥ 65; or aged 19 to 64 with a creatinine clearance < 70 mL/min, history of serious infection or multiple infections in the past two years and/or a CIRS score > 6.
Intervention(s)	Cohort 1 (without del17p) and Cohort 2 (with del17p): oral zanubrutinib 160 mg twice daily (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression.
Comparator(s)	Cohort 1 (without del17p): BR. IV bendamustine over six cycles, 90 mg/m^2/day on the first two days of each cycle and IV rituximab over six cycles, 375 mg/m^2 on Day 0 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 to 6.

	Participants could cross over to oral zanubrutinib 160 mg twice daily (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression as confirmed by IRC.
Location	Australia, Austria, Belgium, Czechia, France, Italy, New Zealand, Poland, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, United States.
Duration of study	NR
Method of randomisation	Participants stratified into one of four cohorts dependent on mutation status. **Cohort 1 (without del17p):** randomised by IRT 1:1 to zanubrutinib or BR, stratified by age (< 65 years versus ≥ 65 years), Binet stage (C versus A or B), IGHV mutational status (mutated versus unmutated), and geographic region (North America versus Europe versus Asia-Pacific). **Cohort 1a (without del17p, China only):** randomised to zanubrutinib or BR; geographic region was not a stratification factor for randomisation. **Cohort 2 (with del17p):** not randomised; zanubrutinib only. **Cohort 3 (with del17p or pathogenic TP53 variant):** non-randomised; zanubrutinib-venetoclax only.
Methods of blinding	Open-label study; the IRC for response assessment was blinded to study treatment. Independent DMC was not blinded. The sponsor did not have access to aggregated data summaries by actual study treatment assignment.
Primary endpoints (including scoring methods and timings of assessments)	PFS measured by IRC in Cohort 1: defined as the time from randomisation to the date of first documentation of IRC-assessed disease progression or death due to any cause (whichever occurs first) using the iwCLL guidelines with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL). Measured on the 7 May 2021 (median follow-up 26.35 months for Arm A, 25.92 months for Arm B (Cohort 1) and 30.52 months for Arm C (Cohort 2)).
Secondary endpoints (including scoring methods and timings of assessments)	ORR measured by IRC and INV in Cohorts 1 and 2: assessed as the proportion of participants achieve a best overall response of CR, CRi, nPR, PR or PRL at or before initiation of subsequent anti-cancer therapy as determined by IRC or INV assessment. OS in Cohort 1: defined as time from randomisation to date of death due to any reason. DOR measured by IRC and INV in Cohorts 1 and 2: defined as the time from the data that criteria for response (i.e., PRL or better) are first met to the date that disease progression is objectively documented, or death, whichever occurs first, as assessed by IRC or INV assessment using the iwCLL guidelines with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL). PFS measured by INV in Cohort 1: defined as the time from randomisation to the date of first documentation of INV-assessed disease progression or death due to any cause (whichever occurs first) using the iwCLL guidelines with modification for treatment-related

	lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL). PROs in Cohort 1: measured as change from baseline in EORTC QLQ-C30 and EQ-5D-5L. PFS measured by IRC and INV in Cohort 2: defined as the time from randomisation to the date of first documentation of IRC-assessed and INV-assessed disease progression or death due to any cause (whichever occurs first) using the iwCLL guidelines with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL). Safety parameters in Cohorts 1 and 2: AEs classified based on MedDRA (Version 24.0) and graded according to the NCI-CTCAE (version 4.03). Pharmacokinetic parameters in Cohort 1 (zanubrutinib arm only) and Cohort 2. All measured on the 7 May 2021 (median follow-up 26.35 months for Arm A, 25.92 months for Arm B (Cohort 1) and 30.52 months for Arm C (Cohort 2)), except OS. OS measured on the 7 March 2022 (median follow-up 36.1 months for Arm A, 35.4 months for Arm B (Cohort 1)).
Source: CS Table 9, CS Table 10 and CS Table 12[6] Abbreviations: AE = Adverse event; BR = Bendamustine-rituximab; CIRS = Cumulative Illness Rating Scale; CLL = Chronic lymphocytic leukaemia; CR = Complete response; CRi = Complete response with incomplete bone marrow recovery; CS = Company submission; CTCAE = Common Terminology Criteria for Adverse Events; del17p = 17p deletion; DMC = Data Monitoring Committee; DOR = Duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; HRQoL = Health-related quality of life; IGHV = Immunoglobulin heavy chain gene; INV = Investigator; IRC = Independent review committee; IV = Intravenous; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; medDRA = Medical Dictionary of Regulatory Activities; mg = Milligram; nPR = Nodular partial remission; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response; PRO = Patient-reported outcome; SLL = Small lymphocytic lymphoma; TTTF = Time to treatment failure.	

The company presented quality assessments for both Cohort 1 (CS, Table 16) and Cohort 2 (CS, Table 17) in the CS.[6] However, the EAG asked the company to provide further justifications for their assessments than was provided in the CS. The company responded with updated quality assessments.[12] Quality assessment of Cohort 1 of the SEQUOIA trial as reported in the clarification letter is presented in Table 3.4, while quality assessment for Cohort 2 as presented in the clarification letter is shown in Table 3.5.[12]

Table 3.4: Quality assessment of Cohort 1 of the SEQUOIA trial as reported in the company's response to the clarification letter

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomised 1:1 using Interactive Response Technology. Randomisation was stratified by a number of factors to reduce imbalance between	Yes

	How is the question addressed?	Grade (yes/no/unclear/NA)
	treatment groups. These techniques minimised the potential for selection bias.	
Was the concealment of treatment allocation adequate?	This was an open-label study. Treatment with zanubrutinib and treatment with BR was open-label; however, the IRC for response assessment was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were the groups similar at the outset of the study in terms of prognostic factors	Baseline demographic and disease characteristics were similar between groups in terms of prognostic factors, with only small differences seen in race and age. See Section B.2a.3.4 of the CS for more detail.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	This was an open-label study. Patients and investigators were not masked to treatment. The IRC for response assessment was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were there any unexpected imbalances in dropouts between groups?	There were no unexpected imbalances in dropouts between groups. See Section B.2a.4.3 of the CS for more detail.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR, therefore there is no evidence to suggest authors measured further outcomes.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the analysis reported ITT analysis, this was appropriate to preserve randomisation and minimise the risk of bias. Appropriate methods were used to account for missing data; missing data were not imputed unless otherwise specified.	Yes

Source: Company response to clarification letter[12]

Abbreviations: BR = Bendamustine-rituximab; CS = Company submission; CSR = Clinical study report; IRC = Independent review committee; ITT = Intention to treat; NA = Not applicable.

Table 3.5: Quality assessment of Cohort 2 of the SEQUOIA trial as reported in the company's response to the clarification letter

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was the cohort recruited in an acceptable way?	Patients were recruited from 160 study locations and allocated to Cohort 2 dependent on mutation status.	Yes
Was the exposure accurately measured to minimise bias?	Extent of exposure, including treatment duration and dose reduction was measured	Yes

	How is the question addressed?	Grade (yes/no/unclear/NA)
	to minimise bias. See Section B.2a.10.1 of the CS for more detail.	
Was the outcome accurately measured to minimise bias?	Outcomes were accurately measured to minimise bias. See Section B.2a.3.3 of the CS for the definition of each outcome measure.	Yes
Have the authors identified all important confounding factors?	All important confounding factors were considered within pre-planned subgroup analyses. See Section B.2a.6 of the CS for more detail.	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes, the authors have considered the impact of potential confiding factors in the analysis, including the potential impact of COVID-19.	Yes
Was the follow-up of patients complete?	See Section B.2a.6 of CS.	Yes
How precise (for example, in terms of confidence interval and p values) are the results?	See Section B.2a.6 of CS.	Yes
Source: Company response to clarification letter[12] Abbreviations: CS = Company submission; NA = Not applicable.		

EAG Comment: The CS states that, while SEQUOIA contains four separate cohorts, only Cohort 1 and Cohort 2 were relevant to the submission. The company stated that Cohort 1a were irrelevant to the submission as they were entirely composed of Chinese participants, which they deemed not representative of the UK population (CS Section B.2a.3.1, p.41).[6] In light of the lack of evidence identified by the company relating to the efficacy of zanubrutinib, the EAG requested that the company provide further rationale for why Cohort 1a was not relevant to the submission in the clarification letter. The company responded that Cohort 1a were not generalisable due to patients with CLL in China generally being younger, with different mutational profiles to the UK and other Western countries.[12] The decision not to include Cohort 1a in the submission was deemed acceptable by the EAG's clinical advisor. Cohort 3 consisted of participants with del17p or TP53 mutation who received a combination of zanubrutinib and venetoclax. The company noted that this was an exploratory cohort and did not assess the effectiveness of zanubrutinib monotherapy, so was not relevant to the appraisal (CS Section B.2a.3.1, p.41).[6] The EAG agrees with the company's assessment that Cohort 3 was not relevant to the appraisal.

As previously detailed in EAG Report Section 2.3, BR is no longer a recommended treatment option for untreated CLL according to the most recent BSH guidelines.[2] However, clinical advice to the EAG noted that BR would still be a reasonable comparator based on previous guidelines. Despite this, the EAG has concerns regarding the use of BR as, for the reasons detailed previously in Section 2.5, the use of BR suggests participants in SEQUOIA Cohort 1 can be considered "fit" as per BSH guidelines. This has implications for the economic model of untreated CLL, which assumed that SEQUOIA trial data were an adequate proxy for the "unfit" population. This issue is discussed further in Section 4.3.3.

The company state in CS Table 9 that OS data from ALPINE was used as an outcome in the economic model for R/R CLL but OS data from SEQUOIA were not used in the economic model for untreated CLL.[6] However, longer follow-up data were available for SEQUOIA (median follow-up for Cohort 1 07 March 2022 data-cut: 36.1 months for Arm A, 35.4 months for Arm B; CS, Table 12) compared with ALPINE (median follow-up for 01 December 2021 data-cut 24.34 months in the zanubrutinib arm and 23.82 months in the ibrutinib arm; CS, Table 31).[6] The EAG asked the company to clarify why OS data from SEQUOIA was not used in the economic model of untreated CLL in the clarification letter. The company responded to state that the data were too immature for OS in SEQUOIA, as there were too few events to provide robust long-term extrapolations.[12] Additionally, the company noted that OS data from SEQUOIA were not used as more detailed subsequent treatment modelling was required in the cost-effectiveness model of untreated CLL.[12] While the company did not use OS data in the economic model, they did use data from SEQUOIA to estimate pre-progression survival (PrePS) (see Section 4.3.6).

In terms of the quality assessment of SEQUOIA Cohorts 1 and 2, the EAG had concerns that the quality assessment of SEQUOIA performed by the company was potentially inadequate. The EAG asked the company to provide further details of the critical appraisal, including which tools were used to make the assessments, the specific method adopted to make the assessments and further justification for all assessments. The company responded by providing more thorough assessments "using the criteria for the assessment of risk of bias and generalisability listed in Section 2.5.2 of the NICE STA user guide,"[12,39] which are replicated in Tables 3.3 and 3.4. The EAG are satisfied that the updated assessments are adequate.

3.2.1.2 Statistical approach adopted for the analysis of SEQUOIA trial data

A summary of the statistical approach taken by the company for analyses within SEQUOIA are presented in CS Table 15.[6] All efficacy analyses were conducted based on the intention-to-treat (ITT) population, which included all enrolled patients who were assigned to a treatment group. The safety analysis set included all patients who received any dose of the study drug.

In Cohort 2, PFS, ORR and DOR were summarised descriptively by both independent review committee (IRC-) and investigator (INV)-assessment. The Kaplan-Meier (KM) method was used to summarise the distribution of PFS and DOR, including quartiles and event-free rates at selected timepoints. An estimate of ORR with 95% Clopper-Pearson confidence intervals (CIs) was generated.[29]

EAG Comment: The company analyses used standard methods. The company provided a prespecified statistical analysis plan and clinical trial protocol at the request of the EAG,[12] which provided a means of cross-validation. There did not appear to be any clear selective reporting of outcomes or analyses in the trial.[29]

3.2.1.3 SEQUOIA eligibility criteria and baseline characteristics including treatments received

A summary of the eligibility criteria for SEQUOIA is detailed in Table 3.6, with baseline characteristics for Cohorts 1 and 2 presented in Table 3.7.

Table 3.6: Eligibility criteria for SEQUOIA study

Inclusion	Exclusion
Unsuitable for treatment with FCR, defined as ≥ 65 years of age at the time of informed consent,	Previous systemic treatment for CLL/SLL

or 18-64 years of age with one of the following factors: • A CIRS score > 6: a baseline CIRS score was not required for enrolment in the trial but, if CIRS score was available, it could have been used to assess eligibility for the trial • Creatinine clearance < 70 mL/min • History of previous serious infection or multiple infections in the past two years	
Confirmed diagnosis of CD20-postitive CLL or SLL that meets iwCLL criteria[7] and requiring treatment as defined by specific criteria	Required ongoing need for corticosteroid treatment
Measurable disease by CT/MRI, with measurable disease defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in two perpendicular diameters	Known prolympocytic leukaemia or history of suspected Richter's transformation
CLL/SLL requiring treatment based on at least one of the iwCLL criteria[7]	Clinically significant cardiovascular disease
ECOG performance status of 0, 1 or 2	Prior malignancy within the past three years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast, or localised Gleason score 6 prostate cancer
Life expectancy ≥ 6 months	History of severe bleeding disorder, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
Adequate bone marrow and organ function by specific criteria	History of stroke or intracranial haemorrhage within six months before first dose of study drug
FISH results from the study-specific central laboratory confirming the presence or absence of del(17p)	Severe or debilitating pulmonary disease
	Active fungal, bacterial, and/or viral infection requiring systemic therapy
	Known central nervous systematic involvement by leukaemia or lymphoma
	Vaccination with a live vaccine within 35 days prior to the first dose of study drug
Source: CS Table 11[6] Abbreviations: CIRS = Cumulative illness rating scale; CLL = Chronic lymphocytic leukaemia; CS = Company submission; CT = Computerised tomography; ECOG = Eastern Cooperative Oncology Group; FCR = Fludarabine-cyclophosphamide-rituximab; FISH = Fluorescence in situ hybridisation; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; MRI = Magnetic resonance imaging; SLL = Small lymphocytic lymphoma.	

Table 3.7: Baseline characteristics of participants in SEQUOIA Cohorts 1 and 2

	Cohort 1		Cohort 2
	BR (N = 238)	**Zanubrutinib (N = 241)**	**Zanubrutinib (N = 111)**
Cancer type, n (%)			
CLL	218 (91.6)	221 (91.7)	100 (90.1)
SLL	20 (8.4)	20 (8.3)	11 (9.9)
Age (years)			
Mean (SD)	69.35 (7.391)	69.82 (7.74)	69.77 (7.75)
Median	70	70	70.00
< 65 years	46 (19.3)	45 (18.7)	16 (14.4)
≥ 65 and < 75 years	139 (58.4)	133 (55.2)	68 (61.3)
≥ 75 years	53 (22.3)	63 (26.1)	27 (24.3)
Sex, n (%)			
Male	144 (60.5)	154 (63.9)	79 (71.2)
Female	94 (39.5)	87 (36.1)	32 (28.8)
Race, n (%)			
White	206 (86.6)	221 (91.7)	105 (94.6)
Not Reported	21 (8.8)	9 (3.7)	4 (3.6)
Asian	9 (3.8)	4 (1.7)	1 (0.9)
Black or African American	1 (0.4)	4 (1.7)	1 (0.9)
Unknown	1 (0.4)	2 (0.8)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)	0 (0.0)
Geographic Region, n (%)			
Europe	172 (72.3)	174 (72.2)	52 (46.8)
Asia Pacific[a]	38 (16.0)	33 (13.7)	47 (42.3)
North America	28 (11.8)	34 (14.1)	12 (10.8)
ECOG Performance Status, n (%)			
0	101 (42.4)	110 (45.6)	44 (39.6)
1	117 (49.2)	116 (48.1)	53 (47.7)
2	20 (8.4)	15 (6.2)	14 (12.6)
Time from initial diagnosis of CLL/SLL to randomisation (months)			
Mean (SD)	38.64 (38.60)	47.62 (49.67)	40.54 (55.33)
Median	28.67	31.28	21.39
Binet stage at study entry for CLL, n (%)			
A	28 (12.8)	30 (13.6)	14 (14.0)
B	124 (56.9)	126 (57.0)	49 (49.0)
C	66 (30.3)	65 (29.4)	37 (37.0)
Del17p, n (%)			

	Cohort 1		Cohort 2
	BR (N = 238)	**Zanubrutinib (N = 241)**	**Zanubrutinib (N = 111)**
Yes	0 (0.0)	2 (0.8)[b]	110 (99.1)[c]
No	238 (100.0)	239 (99.2)	1 (0.9)
TP53 mutation, n (%)			
Yes	13 (5.5)	15 (6.2)	47 (42.3)
No	210 (88.2)	217 (90.0)	62 (55.9)
Missing	15 (6.3)	9 (3.7)	2 (1.8)
Del17p or TP53 mutation, n (%)			
Yes	13 (5.5)	17 (7.1)	110 (00.1)
No	225 (94.5)	224 (92.9)	1 (0.9)
IGHV mutational status, n (%)			
Mutated	110 (46.2)	109 (45.2)	36 (32.4)
Unmutated	121 (50.8)	125 (51.9)	67 (60.4)
Undetermined	7 (3.0)	7 (2.9)	8 (7.2)
β_2 microglobulin, n (%)			
Mean (SD)	4.97 (6.94)	4.49 (3.19)	5.16 (2.20)
≤ 3.5 mg/L	98 (41.2)	99 (41.1)	23 (20.7)
> 3.5 mg/L	131 (55.0)	135 (56.0)	78 (70.3)

Source: CS, Tables 13 and 14[6]
[a] CS Table 13 and 14 footnotes state that Asia Pacific refers to Australia, New Zealand, Korea, China and Taiwan
[b] CS Table 13 footnotes state that these participants were inadvertently included in this arm of the study
[c] CS Table 14 footnotes state that one participant without del17p was included in Cohort 2 due to site error but was not included in the efficacy analysis
Abbreviations: BR = Bendamustine-rituximab; CLL = Chronic lymphocytic leukaemia; CS = Company submission; ECOG = Eastern Cooperative Oncology Group; IGHV = Immunoglobulin heavy chain variable region; PS = Performance status; SD = Standard deviation; SLL = Small lymphocytic lymphoma.

EAG Comment: The eligibility criteria for SEQUOIA contained some ambiguities that the EAG asked the company to clarify. Firstly, the EAG asked the company to clarify their definition of "clinically significant cardiovascular disease" and to further define "severe or debilitating pulmonary disease" in the clarification letter. The company responded that details were contained within the SEQUOIA clinical study report (CSR) and provided this information in the reference pack.[12] The EAG were satisfied that the inclusion criteria were appropriate.

Furthermore, the EAG asked the company to clarify whether there was a limit on the number of comorbidities that a participant in SEQUOIA could have and whether there was a limit on the number of medications that potential participants could be taking in the clarification letter. The company responded that details were contained within the SEQUOIA protocol and SAP, which were provided in the reference pack.[12]

[redacted]

Further information on the number of comorbidities and concomitant medications reported in the SEQUOIA trial were provided by the company in their response to the clarification letter. The company did not provide a mean estimate per arm in their response.[12] However, the company did state that one or more comorbidities were reported in [redacted] participants in the zanubrutinib arm and [redacted] participants in the BR arm in Cohort 1, while in Cohort 2 comorbidities were reported in [redacted] participants.[12] Additionally, the company stated that almost all participants in Cohort 1 received at least one concomitant medication ([redacted] in the zanubrutinib arm and [redacted] in the BR arm), with the most common medications being antibacterial medications for systemic use, analgesics, antigout preparations and corticosteroids for systemic use.[12] Similarly, the company also reported that nearly all participants in Cohort 2 ([redacted]) received at least one concomitant medication, with the most common medications being antibacterial for systemic use, analgesics, agents acting on the renin-angiotensin system, antigout preparations and antithrombotic agents.[12] Following clinical advice, the EAG were satisfied that this reflected the general characteristics of the population seen in clinical practice.

Overall, the distribution of characteristics between the zanubrutinib and BR arm in Cohort 1 was generally well-balanced, though the company noted small differences in race and age, as well as a small proportion of participants inadvertently added to Cohort 1 prior to mutation screening (CS Section B.2a.3.4, p.46).[6] With the exception of del17p status, participants in Cohort 2 were generally similar to those in Cohort 1, though more participants were recruited from the Asia-Pacific region; most of these participants (> 90% across Cohorts 1 and 2) were enrolled in Australia or New Zealand (CS Section B.2a.3.4, p.48).[6]

The EAG asked the company to clarify how many of the 65 participants from the UK were randomised in Cohort 1 or included in Cohort 2. In response, the company noted that there was a typographical error in the CS and that 64 participants were enrolled from UK sites.[12] Of these, [redacted] were enrolled in the zanubrutinib arm of Cohort 1, [redacted] in the BR arm of Cohort 1 and [redacted] in Cohort 2, with the remaining [redacted] enrolled into Cohort 3.[12]

3.2.1.4 SEQUOIA efficacy

The efficacy of zanubrutinib in Cohorts 1 and Cohort 2 of relevance to the decision problem and economic model of untreated CLL are shown in Table 3.8.[6] In Cohort 1, the median follow-up in the zanubrutinib arm was 26.35 months and in the BR arm median follow-up was 25.92 months (CS Section B.2a.4.3, p.54).[6] The median follow-up in Cohort 2 was 30.52 months (CS Section B.2a.4.3, p.56).[6]

Table 3.8: Key efficacy outcomes in SEQUOIA Cohorts 1 and 2

	Cohort 1		Cohort 2
	Zanubrutinib (N= 241)	**BR (N= 238)**	**Zanubrutinib (N= 110)**
IRC-assessed PFS (DCO 07 May 2021)			
Events, n (%)	36 (14.9)	71 (29.8)	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI) [p-value][a]	0.42 (0.28, 0.63) [p<0.0001]		-
Event-free rate at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]

Event-free rate at 18 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 30 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 36 months, % (95% CI)	[redacted]	[redacted]	[redacted]
INV-assessed PFS (DCO 07 May 2021)			
Events, n (%)	29 (12.0)	57 (23.9)	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI) [p-value] [a]	0.42 (0.27, 0.66) [p<0.0001]		-
Event-free rate at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 18 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 30 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 36 months, % (95% CI)	[redacted]	[redacted]	[redacted]
IRC-assessed ORR (DCO 07 May 2021)			
ORR, n (%) [95% CI]	228 (94.6) [91.0, 97.1]	203 (85.3) [80.1, 89.5]	99 (90.0) [82.8, 94.9]
OR (95% CI) [p-value] [a]	[redacted]		-
INV-assessed ORR (DCO 07 May 2021)			
ORR, n (%) [95% CI]	235 (97.5) [94.7, 99.1]	211 (88.7) [83.9, 92.4]	106 (96.4) [91.0, 99.0]
OR (95% CI) [p-value] [a]	[redacted]		-
OS (DCO 07 March 2022)			
Events, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI) [p value]	[redacted]		-
Event-free rate at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 18 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 30 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 36 months, % (95% CI)	[redacted]	[redacted]	[redacted]

IRC-assessed response (DCO 07 May 2021)			
Complete response, n (%)	16 (6.6)	36 (15.1)	7 (6.4)
Nodular partial remission (Npr), n (%)	3 (1.2)	14 (5.9)	2 (1.8)
Partial response, n (%)	206 (85.5)	153 (64.3)	88 (80.0)
Partial response with lymphocytosis, n (%)	3 (1.2)	0 (0.0)	2 (1.8)
Stable disease, n (%)	7 (2.9)	14 (5.9)	11 (10.0)
Not evaluable, n (%)	1 (0.4)	1 (0.4)	NR[a]
Discontinued prior to first assessment, n (%)	3 (1.2)	19 (8.0)	NR[a]
INV-assessed response (DCO 07 May 2021)			
Complete response, n (%)	22 (9.1)	43 (18.1)	10 (9.1)
Complete response with incomplete bone narrow recovery (CRi), n (%)	0 (0.0)	1 (0.4)	NR[b]
Nodular partial remission (Npr), n (%)	5 (2.1)	18 (7.6)	4 (3.6)
Partial response, n (%)	204 (84.6)	149 (62.6)	91 (82.7)
Partial response with lymphocytosis, n (%)	4 (1.7)	0 (0.0)	1 (0.9)
Stable disease, n (%)	3 (1.2)	5 (2.1)	3 (2.7)
Progressive disease (PD), n (%)	0 (0.0)	1 (0.4)	1 (0.9)
Not evaluable, n (%)	0 (0.0)	1 (0.4)	NR[b]
Discontinued prior to first assessment, n (%)	3 (1.2)	20 (8.4)	NR[b]
IRC-assessed DOR (DCO 07 May 2021)			
Events, n (%)	[redacted]	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Median DOR, months (95% CI)	NE (NE, NE)	30.6 (25.5, NE)	[redacted]
Event-free rate at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 18 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 30 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 36 months, % (95% CI)	[redacted]	[redacted]	[redacted]
INV-assessed DOR (DCO 07 May 2021)			

Events, n (%)	[redacted]	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Median DOR, months (95% CI)	NE (NE, NE)	30.6 (26.2, NE)	[redacted]
Event-free rate at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 18 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 30 months, % (95% CI)	[redacted]	[redacted]	[redacted]
Event-free rate at 36 months, % (95% CI)	[redacted]	[redacted]	[redacted]

Source: CS Table 18, Table 21, Table 19, Table 22, Table 23, Table 25, Table 26, Table 27, Table 28,[6] CS section B.2a.6.3 (p.65)[6]
[a] Footnotes to CS Table 18 state that HR and 95% CI were from stratified Cox regression models with BR arm as the reference group
[b] Not reported in CS Table 25
Abbreviations: BR = Bendamustine-rituximab; CI = Confidence interval; CRi = Complete response with incomplete bone narrow recovery; CS = Company submission; DOR = Duration of response; INV = Investigator; IRC = Independent review committee; NE = Not estimable; Npr = Nodular partial remission; NR = Not reported; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival.

The company performed sensitivity analyses on the primary endpoint of PFS by IRC for SEQUOIA Cohort 1 by unstratified analysis, being based on the per protocol analysis set, by initiation of any non-protocol CLL/SLL-related therapy treated as a PFS event and death or disease progression immediately after two or more missed consecutive disease assessments treated as a PFS event (CS Section B.2a.6.2, p.62-3).[6] The company stated that there were no statistically significantly different results for any of these sensitivity analyses compared with the primary analysis.

EAG Comment: As previously stated in EAG Report Section 2.4, the company noted in their response to the clarification letter that the inclusion of TTTF as an outcome in SEQUOIA was a typographical error and that these data are not available for SEQUOIA.[12] Therefore, SEQUOIA does not report on all outcomes of relevance to the NICE decision problem (see Table 2.1 and Section 2.4).

For Cohort 1, the company demonstrated non-inferiority for PFS and response rate; zanubrutinib was superior to BR for these outcome measures. However, non-inferiority was not established for OS, as the 95% confidence intervals (CIs) crossed the line of no effect and the upper limit of the CI contained a clinically important difference. As non-inferiority was not established for all key efficacy outcomes, the EAG does not consider that the requirement required to undertake a valid cost-minimisation analysis (CMA) of untreated CLL have been met.[41] Further critique in relation to the economic model is provided in Section 4.3.6.2.

It was unclear from the CS whether the sensitivity analyses for PFS by IRC in Cohort 1 of SEQUOIA were pre-planned within the protocol. As such, the EAG asked the company whether the sensitivity analyses were pre-planned or post-hoc analyses. The company responded that these details were contained within the protocol for SEQUOIA, which was provided in the reference pack alongside

their response to the clarification letter.[12] The EAG confirmed from these documents that all sensitivity analyses were pre-planned and therefore had no concerns.[40,42]

3.2.1.5 Participant-reported outcomes in SEQUOIA

Participant-reported outcomes (PROs) were only assessed in SEQUOIA Cohort 1 (CS, Table 24).[6] The company reported that least squares mean change from baseline in EORTC QLQ-C30 domain scores whereby, according to the EORTC QLQ-C30 manual referenced by the company in their responses to the clarification letter, scores range from 0 to 100 and higher scores indicate a higher level of response.[43] The company reported that there were significant improvements in the zanubrutinib arm at week 24 in global health score (GHS) ([redacted]), physical function ([redacted]), role functioning ([redacted]), fatigue ([redacted]), nausea/vomiting ([redacted]) and diarrhoea ([redacted]) compared with the BR arm.[6] The LS difference between the two arms in pain was significant at Week 12 ([redacted]) but not at Week 24 (CS, Table 24).[6]

The EAG requested in the clarification letter that the company provide raw data in the form of mean EORTC QLQ-C30 scores at baseline, week 12 and week 24 in addition to the change scores presented in CS Table 24, as well as any data available beyond week 24. The company provided data for baseline, week 12 and week 24, which is reported in Table 3.9.[12]

Table 3.9: Mean EORTC QLQ-C30 scores in Cohort 1 of SEQUOIA as documented in company's response to the clarification letter

PRO endpoint	Zanubrutinib			BR		
	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
GHS/QoL	[redacted]					
Physical function	[redacted]					
Role function	[redacted]					
Fatigue	[redacted]					
Nausea/ Vomiting	[redacted]					
Diarrhoea	[redacted]					
Pain	[redacted]					

Source: Company response to clarification letter[12]
Abbreviations: BR = Bendamustine-rituximab; GHS = Global health status; PRO = Patient-reported outcome; QoL = Quality of life.

Additionally, the company provided data on GHS/QoL EORTC QLQ-C30 scores in Cohort 1 of SEQUOIA from weeks 36 to 144.[12] These data are presented in Table 3.10.

Table 3.10: Mean GHS/QoL scores on EORTC QLQ-C30 from week 36 in SEQUOIA

GHS/QoL	Zanubrutinib (N=241)	BR (N=238)
Week 36	[redacted]	[redacted]
Week 48	[redacted]	[redacted]
Week 60	[redacted]	[redacted]
Week 72	[redacted]	[redacted]
Week 84	[redacted]	[redacted]
Week 96	[redacted]	[redacted]
Week 120	[redacted]	[redacted]
Week 144	[redacted]	[redacted]

Source: Company response to clarification letter[12]
Abbreviations: BR = Bendamustine-rituximab; GHS = Global health score; QoL = Quality of life.

The CS narratively reported on mean improvements and standard deviation (SD) in the visual analogue scale (VAS) of the EQ-5D VAS at week 12 (zanubrutinib: [redacted]; BR: [redacted]) and week 24 (zanubrutinib: [redacted]; BR: [redacted]) (CS Section B.2a.6.3, p. 68).[6] No further information on the EQ-5D (either VAS or utility scores) was reported in this section of the CS.

EAG Comment: The company stated that there were significant improvements in some EORTC QLQ-C30 domains when measured using least squares mean change scores from baseline. However, the EAG has concerns relating to this estimation, as it was unclear to the EAG how the least squares mean was estimated and whether the company controlled for potential baseline imbalances between zanubrutinib and BR.[6] Additionally, the width of the 95% CIs for GHS, role functioning, fatigue and nausea/vomiting all crossed the line of no effect, indicating a lack of statistical significance. It is unclear whether data are sufficiently precise to rule out clinically meaningful differences between groups.

In addition to further information about EORTC QLQ-C30 scores reported above, the EAG requested that mean overall scores for the EORTC QLQ-C30 at each timepoint were provided. The company did not provide a total score as they stated that the EORTC QLQ-C30 user manual cautions against the use of the sum of all items and suggests that GHS/QoL should be used as an overall summary measure.[12,43] The EAG is satisfied with this rationale.

The EAG requested that the company provide descriptive summaries (including mean and measure of variance) for the EQ-5D utility data for each time-point in the clarification letter. The company responded by providing data for SEQUOIA Cohort 1 at baseline, cycle one and response assessments between weeks 12 and 144.[12] These data are discussed in further detail in Section 4.3.8.

The EAG cannot comment on the EQ-5D VAS scores presented as the company only narratively described improvements in the scale at 12 and 24 weeks; the EAG assume that these changes reflect improvements from baseline.[6]

The company did not report on PROs for Cohort 2 of SEQUOIA as the study design states that they only planned to report PROs for Cohort 1 (CS, Table 10).[6] Therefore, the EAG cannot comment

further on HRQoL for Cohort 2; this has an implication for the economic analysis, as utilities for the high-risk population are not available (see Section 4.3.8).

3.2.1.6 Adverse events in SEQUOIA

The company reported on Grade 3 or higher treatment-emergent adverse events (TEAEs) or post-treatment AEs reported in ≥ 2% of participants in SEQUOIA in CS Table 62 (Section B.2a.10.2, p.149).[6] These data for SEQUOIA Cohorts 1 and 2 are presented in Table 3.11.

Table 3.11: Grade 3 or higher treatment-emergent and post-treatment adverse events reported in ≥ 2% of participants in SEQUOIA

Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One AE of Grade 3 or Higher	181 (79.7)	126 (52.5)	61 (55.0)
Neutropenia	94 (41.4)	22 (9.2)	12 (10.8)
Hypertension	11 (4.8)	15 (6.3)	5 (4.5)
COVID-19	2 (0.9)	11 (4.6)	1 (0.9)
COVID-19 pneumonia	0 (0.0)	7 (2.9)	2 (1.8)
Neutrophil count decreased	24 (10.6)	5 (2.1)	5 (4.5)
Pneumonia	10 (4.4)	4 (1.7)	6 (5.4)
Thrombocytopenia	16 (7.0)	4 (1.7)	1 (0.9)
Febrile neutropenia	17 (7.5)	2 (0.8)	1 (0.9)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Urinary tract infection	6 (2.6)	2 (0.8)	2 (1.8)
Atrial fibrillation	3 (1.3)	1 (0.4)	4 (3.6)
Fall	2 (0.9)	1 (0.4)	3 (2.7)
Hypotension	5 (2.2)	1 (0.4)	2 (1.8)
Infusion related reaction	6 (2.6)	0 (0.0)	0 (0.0)
Leukopenia	5 (2.2)	0 (0.0)	0 (0.0)
Pyrexia	8 (3.5)	0 (0.0)	1 (0.9)
Rash	6 (2.6)	0 (0.0)	0 (0.0)

Source: CS, Table 62[6]
Abbreviations: AE = Adverse event; BR = Bendamustine-rituximab; CS = Company submission; TEAE = Treatment-emergent adverse event.

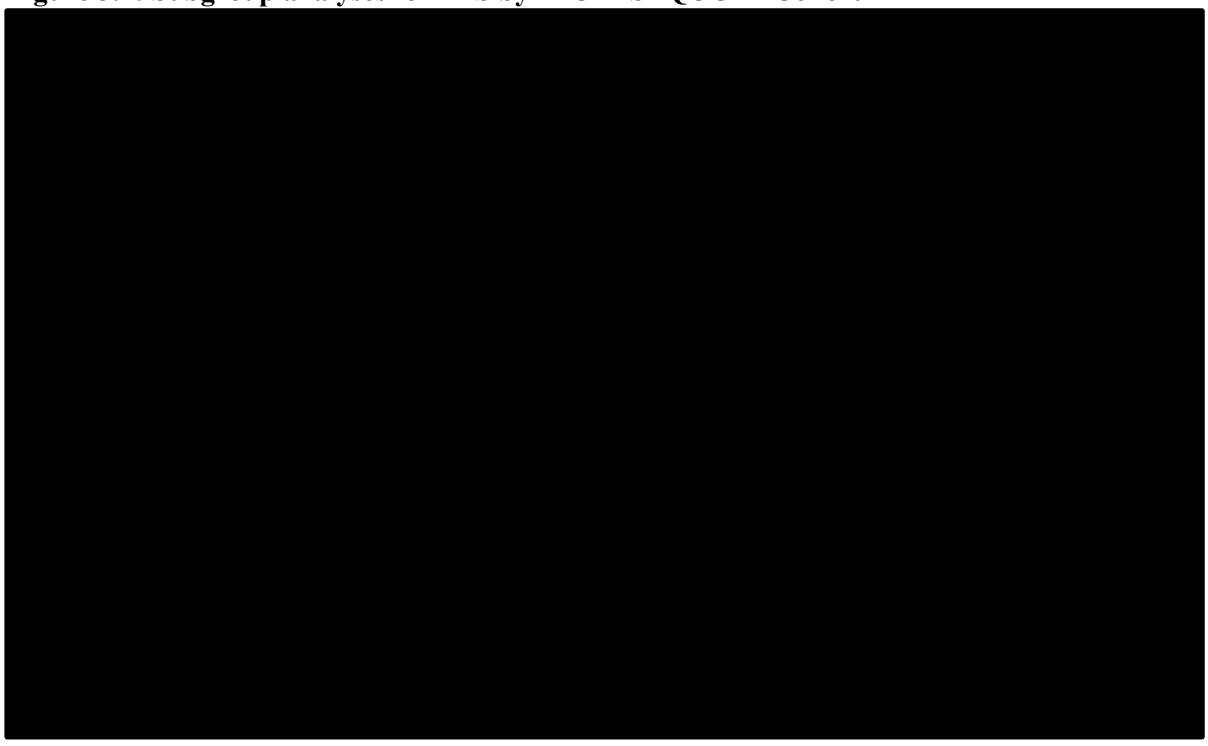
The company stated that five participants (2.1%) in the zanubrutinib arm of Cohort 1 discontinued treatment due to COVID-19 related AEs (CS Section B.2a.4.3, p.54).[6] Fatal COVID-19 AEs were observed in five (2.1%) participants in the zanubrutinib arm and one participant (0.4%) in the BR arm of Cohort 1 (CS Section B.2a.4.3, p.54).[6] In Cohort 2, no participant discontinued treatment due to COVID-19 related AEs, though three participants experienced dose interruption (CS Section B.2a.4.3, p.56).[6]

EAG Comment: The EAG asked the company to clarify why there was a discrepancy in the proportion of AEs reported between untreated and R/R CLL in the clarification letter. The company responded that the R/R population were more likely to suffer from AEs so a lower limit of 2% proportion experiencing Grade 3 or more TEAEs was placed on this population.[12] However, there is a discrepancy in the CS between what is reported in the clinical effectiveness results and the economic model for the untreated population. In the clinical effectiveness section, Grade 3 or higher TEAEs or post-treatment AEs reported in ≥ 2% of participants in SEQUOIA were reported (CS, Table 62).[6] However, in the economic model Grade 3 or more TEAEs occurring in ≥ 1% of patients by treatment was reported (CS, Table 79).[6] It is unclear to the EAG, both from the CS and the company's response to the clarification letter, why this discrepancy exists.

3.2.1.7 Subgroup analyses in SEQUOIA

The company reported subgroup analyses for IRC-assessed PFS in Cohort 1 of SEQUOIA in the CS (Section B.2a.7).[6] The company stated that there were statistically significant benefits for zanubrutinib compared with BR in: participants with 11q deletion; participants serum β_2 microglobulin greater than 3.5mg/L; participants with IGHV unmutated; and participants with bulky disease of 5 cm or greater (CS Section B.2a.7, p.74).[6] Full subgroup analyses as presented in the CS are detailed in Figure 3.1.

Figure 3.1: Subgroup analyses for PFS by IRC in SEQUOIA Cohort 1



Source: CS Figure 12 (Section B.2a.7, p.74)[6]

[a] CS states that HRs and 95% CIs were from stratified (for all patients) or unstratified (for subgroup) analysis Cox regression model with BR arm as the reference group

[b] CS states cytopenia is participants having anaemia or thrombocytopenia or neutropenia

[c] CS states based on monosomy 13q mutation results

Abbreviations: BR = Bendamustine-rituximab; CI = Confidence interval; CLL = Chronic lymphocytic leukaemia; CS = Company submission; ECOG = Eastern Cooperative Oncology Group; HR = Hazard ratio; IGHV = Immunoglobin heavy chain gene; IRC = Independent review committee; LDi = Longest diameter; PFS = Progression-free survival; SLL = Small lymphocytic leukaemia.

EAG **Comment**: [redacted] As such, although the company stated in the CS that there was a statistically significant benefit in favour of zanubrutinib for participants with unmutated IGHV (CS Section B.2a.7, p.74),[6] the EAG believes there is uncertainty surrounding this subgroup analysis due to the potentially reduced efficacy of CIT (including BR) in this subpopulation.

In CS Table 10, the company state that geographic region, LDH, 13q deletion, complex karyotype and trisomy 12 were listed as prespecified subgroup for SEQUOIA.[6] However, these specific subgroups were not presented in CS Figure 12.[6] The EAG asked the company to clarify the rationale behind not performing these subgroups and to provide the data for these subgroups. The company responded that these were described in the clinical trial protocol and SAP for SEQUOIA, which was provided to the EAG.[12,40,42] [redacted]. As such, it is also unclear to the EAG whether this is a plausible source of bias.

3.2.2 ALPINE trial

3.2.2.1 ALPINE trial design and quality assessment

The evidence of the effectiveness of zanubrutinib compared with ibrutinib was derived from the ALPINE trial (NCT03734016).[6,30,38] This is a phase III, ongoing, parallel-arm, open-label study in 652 adults with R/R CLL that met the iwCLL criteria, relapsed or refractory to at least one prior systemic therapy for CLL. Randomisation was stratified by age, geographic location, mutation status and refractory status. The ALPINE trial planned to report on ORR, PFS, OS, TTTF, AEs and HRQoL, with PFS, OS, AEs and HRQoL used in the economic model (see Section 4.4). A summary of the ALPINE trial methodology is shown in Table 3.12.

Table 3.12 ALPINE study design

Category of design	Details
Trial design	Phase 3, open-label, randomised, multicentre
Population	Patients ≥18 years with a diagnosis of CLL/SLL that met the iwCLL criteria, relapsed or refractory to at least one prior systemic therapy for CLL/SLL
Intervention(s)	Arm A: Oral zanubrutinib 160 mg twice a day (two 80 mg capsules twice a day) until unacceptable toxicity or disease progression.
Comparator(s)	Arm B: Oral ibrutinib 420 mg once a day (three 140 mg capsules once a day) until unacceptable toxicity or disease progression.
Location	Australia, Belgium, China, Czechia, France, Germany, Italy, Netherlands, New Zealand, Poland, Spain, Sweden, Turkey, United Kingdom
Duration of study	NR
Method of randomisation	IRT was used to randomise patients 1:1 to either zanubrutinib or ibrutinib. Randomisation was stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/TP53 mutation status (present or absent)

Methods of blinding	This was an open-label study; however, the IRC for response assessment was blinded to study treatment. Whilst the independent DMC was not blinded due to the open-label nature of the study, the sponsor did not have access to aggregated data summaries by actual study treatment assignment while the study was ongoing to avoid unwanted bias.
Primary endpoints (including scoring methods and timings of assessments)	ORR measured by INV in Cohort 1: defined as the proportion of patients achieving a best overall response of CR, CRi, nPR or PR determined by INV assessment using the iwCLL guidelines with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL) Measured at 1 December 2021 (median follow-up 24.34 months for arm A, 23.82 months for arm B).
Secondary endpoints (including scoring methods and timings of assessments)	PFS measured by IRC and INV[a]: defined as the time from randomisation to the date of first documentation of disease progression or death, whichever occurred first, as determined by INV or IRC assessment Safety parameters: AEs classified based on MedDRA (Version 20.0 or higher) and graded according to the NCI-CTCAE (version 4.03) DOR measured by IRC and INV: defined as time from the date that response criteria were first met to the date that disease progression was objectively documented or death, whichever occurs first, as determined by INV or IRC assessment TTTF: defined as time from randomisation to discontinuation of study drug due to any reason OS: Time from randomisation to the date of death due to any cause PROs: measured as change from baseline in EORTC QLQ-C30 and EQ-5D-5L scores All measured at 1 December 2021 (median follow-up 24.34 months for arm A, 23.82 months for arm B) except PFS. PFS measured at 1 December 2021 (median follow-up 24.34 months for arm A, 23.82 months for arm B) and 08 August 2022 (median follow-up 32.00 months in arm A and 27.89 months in arm B

Source: CS, Table 29 and Table 31[6]

[a] INV-assessed PFS and the incidence of treatment-emergent atrial fibrillation/flutter were reported as key secondary outcomes of interest.

Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; CR = Complete response; CRi = Complete response with incomplete bone marrow recovery; CTCAE = Common Terminology Criteria for Adverse Events; DMC = Data Monitoring Committee; DOR = Duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; HRQoL = Health-related quality of life; IGHV = Immunoglobulin heavy chain gene; INV = Investigator assessed; IRC = Independent central review; IRT = Interactive Response Technology; IV = Intravenous; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; medDRA = Medical Dictionary of Regulatory Activities; mg = Milligram; nPR = Nodular partial remission; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response; PRO = Patient-reported outcome; SLL = Small lymphocytic lymphoma; TTTF = Time to treatment failure.

Quality assessment of the ALPINE trial was presented in the CS (Table 34).[6] However, the EAG asked the company to provide further justifications for their assessments than was provided in the CS. The company responded with an updated quality assessment.[12] Quality assessment as reported by the company in the clarification letter is presented in Table 3.13.[12]

Table 3.13: Quality assessment of the ALPINE trial as reported in the CS

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomised 1:1 using Interactive Response Technology. Randomisation was stratified by a number of factors to reduce imbalance between treatment groups. These techniques minimised the potential for selection bias.	Yes
Was the concealment of treatment allocation adequate?	This was an open-label study. Treatment with zanubrutinib and treatment with ibrutinib was open-label; however, the IRC for response assessment was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were the groups similar at the outset of the study in terms of prognostic factors	Baseline demographic and disease characteristics were similar between groups in terms of prognostic factors, with only small differences were seen in sex and age. See Section B.2b.3.4 of the CS for more detail.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	This was an open-label study. Patients and investigators were not masked to treatment. The IRC was blinded to study treatment, hence minimising the risk of bias in outcome assessment.	No
Were there any unexpected imbalances in dropouts between groups?	There were no unexpected imbalances in dropouts between groups. See Section B.2b.4.3 of the CS Participant flow.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR, therefore there is no evidence to suggest authors measured further outcomes.	No

	How is the question addressed?	Grade (yes/no/unclear/NA)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analysis reported ITT analysis, this was appropriate to preserve randomisation and minimise the risk of bias. Appropriate methods were used to account for missing data; missing data were not imputed unless otherwise specified.	Yes
Source: Company response to clarification letter[12] Abbreviations: CS = Company submission; CSR = Clinical study report; IRC = Independent review committee; ITT = Intention-to-treat.		

EAG Comment: The EAG agreed that the inclusion of the ALPINE trial was useful for decision making. The trial was randomised, had an adequate sample size and evaluated the intervention and comparator detailed in the NICE scope.[17]

There is some concern regarding risk of bias due to the open label trial design. It is unclear whether knowledge of the intervention may have impacted treatment and subsequently impacted the PROs.

The EAG asked the company to provide further details of the critical appraisal, including which tools and methods were used to perform the critical appraisal, and further justification for all risk of bias judgements made in the clarification letter. The company's response stated they had used the criteria for the assessment of risk of bias and generalisability listed in Section 2.5.2. of the NICE STA user guide.[12,39] The company also responded to the EAG request by providing thorough reasoning for each risk of bias assessment made. The EAG are satisfied that the updated assessments are adequate, as knowledge of the intervention would not have a significant impact on the outcomes reported.

The company did not state the comorbidities the included patients had at study onset, which the EAG considered important in the R/R CLL population. In the clarification letter, the EAG requested further information on the comorbidities reported by participants split by randomised arm. The EAG also requested the list of prior lines of treatment participants received before being randomised to ALPINE, as an inclusion criterion for the trial was for patients who had received at least one prior line of systemic therapy. The company provided a list of common comorbidities in Table 3 of the company's response to the clarification letter and detailed the full list of concomitant medications used by the participants in Table 14.1.2.6 in the ALPINE CSR, providing this information in the reference pack.[12] The EAG are satisfied that the comorbidities participants presented at commencement of the ALPINE trial would not have affected the results of the trial.

3.2.2.2 Statistical approach adopted for the analysis of ALPINE study data

A summary of the statistical approach taken by the company for analyses within ALPINE are presented in CS Table 33.[6] The outcomes reported included ORR, PFS, OS, DOR, TTF, HRQoL (EORTC QLQ-C30) and AEs. All efficacy analyses were conducted based on the ITT population, which included all enrolled participants who were assigned to a treatment group. The safety analysis set included all participants who received any dose of the study drug.

EAG Comment: The company analyses use standard methods. The company provided a prespecified statistical analysis plan and clinical trial protocol at the request of the EAG.[12] There did not appear to be any clear selective reporting of outcomes or analyses in the trial, or any other areas of concern.[30]

3.2.2.3 ALPINE eligibility criteria and baseline characteristics including treatments received

A summary of the eligibility criteria for ALPINE is detailed in Table 3.14, with baseline characteristics presented in Table 3.15.

Table 3.14: Eligibility criteria for ALPINE study

Inclusion	Exclusion
Age 18 years or older	Known prolymphocytic leukaemia or history of, or suspected, Richter's transformation
Confirmed diagnosis of CLL or SLL that met the iwCLL criteria [7] and requiring treatment as defined by specific criteria	Clinically significant cardiovascular disease
R/R to at least one prior systemic therapy for CLL/SLL	Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast
Measurable disease by CT/MRI, with measurable disease defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters or an extranodal lesion > 10 mm in longest perpendicular diameter	History of severe bleeding disorder, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
ECOG performance status of 0, 1 or 2	History of stroke or intracranial haemorrhage within 180 days before first dose of study drug
Life expectancy ≥ 6 months	Severe or debilitating pulmonary disease
Adequate bone marrow and organ function by specific criteria	Active fungal, bacterial, and/or viral infection requiring systemic therapy
Adequate renal and hepatic function	Known central nervous system involvement by leukaemia or lymphoma
	Prior treatment with BTKi
	Vaccination with a live vaccine within 35 days prior to the first dose of study drug

Source: CS, Table 30[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CS = Company submission; BTKi = Bruton tyrosine kinase inhibitor; CT = Computerised tomography; ECOG = European Cooperative Oncology Group; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; MRI = Magnetic resonance imaging; R/R = Relapsed/refractory; SLL = Small lymphocytic lymphoma.

Table 3.15: Baseline characteristics of participants in ALPINE

	Zanubrutinib (N=327)	Ibrutinib (N=325)
Cancer type, n (%)		
CLL	314 (96.0)	309 (95.1)
SLL	13 (4.0)	16 (4.9)
Age (years)		
Mean (SD)	66.7 (10.18)	67.1 (9.18)
Median	67.0	68.0
< 65 years	126 (38.5)	125 (38.5)
≥ 65 and < 75 years	127 (38.8)	131 (40.3)
≥ 75 years	74 (22.6)	69 (21.2)
Sex, n (%)		
Male	213 (65.1)	232 (71.4)
Female	114 (34.9)	93 (28.6)
Race, n (%)		
White	261 (79.8)	270 (83.1)
Asian	47 (14.4)	44 (13.5)
Unknown[a]	9 (2.8)	7 (2.2)
Other	10 (3.1)	4 (1.2)
Geographic Region, n (%)		
Europe	198 (60.6)	191 (58.8)
Asia	49 (15.0)	45 (13.8)
North America	52 (15.8)	59 (18.2)
Australia/New Zealand	28 (8.6)	30 (9.2)
ECOG Performance Status, n (%)		
0-1	320 (97.9)	312 (96.0)
2	7 (2.1)	13 (4.0)
Time from initial diagnosis of CLL/SLL to randomisation (months)		
Mean (SD)	90.0 (55.07)	94.1 (60.43)
Median	83.5	82.0
Binet stage at study entry for CLL, n (%)		
A/B	182 (55.7)	189 (58.2)
C	145 (44.3)	135 (41.5)
Missing	0 (0.0)	1 (0.3)
Del17p, n (%)		
Yes	45 (13.8)	50 (15.4)
No	282 (86.2)	275 (84.6)
TP53 mutation, n (%)		
Yes	50 (15.3)	45 (13.8)

	Zanubrutinib (N=327)	Ibrutinib (N=325)
No	276 (84.4)	280 (86.2)
Missing	1 (0.3)	0 (0.0)
Del17p or TP53 mutation status, n (%)		
Yes	75 (22.9)	75 (23.1)
No	251 (76.8)	250 (76.9)
Missing	1 (0.3)	0 (0.0)
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Missing	9 (2.8)	16 (4.9)
β_2 microglobulin, n (%)		
≤ 3.5 mg/L	104 (31.8)	92 (28.3)
> 3.5 mg/L	177 (54.1)	183 (56.3)
Missing	46 (14.1)	50 (15.4)

Source: CS, Table 32[6]
[a] Unknown = Unknown or not reported. Other = Other, multiple, black or African American, or Native Hawaiian or Other Pacific Islander.
Abbreviations: CLL = Chronic lymphocytic leukaemia; CS = Company submission; ECOG = Eastern Cooperative Oncology Group; SD = Standard deviation; SD = Standard deviation; SLL = Small lymphocytic lymphoma.

Additionally, the company also provided the number of prior lines of systemic therapy the trial participants had received before study treatment initiation in the response to the EAG.[12] This is presented in Table 3.16.

Table 3.16: Prior lines of systemic therapy in ALPINE

Number of prior lines of systemic therapy, n (%)	Zanubrutinib (N=327)	Ibrutinib (N=325)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
≥ 6	[redacted]	[redacted]

Source: Company response to clarification letter[12]
Abbreviations: n = Number of prior lines; N = Number of participants.

EAG Comment: The eligibility criteria for the ALPINE trial contained some ambiguities that the EAG asked the company to clarify. Advice from the EAG's clinical expert suggested that participants on warfarin would be ineligible to take part, as BTKis are typically contraindicated alongside warfarin. Additionally, cardiac arrhythmias, bleeding conditions, heart attack or coronary stenting within the last year may all preclude BTKi use. As such, the EAG asked the company to clarify their definition of

"clinically significant cardiovascular disease" in the clarification letter. The EAG also asked the company to further define "severe or debilitating pulmonary disease".[12] The company responded that details were contained within the ALPINE CSR and provided this information in the reference pack.[12] Although the ALPINE CSR did not provide a definition for "severe or debilitating pulmonary disease," it provided the definition for "clinically significant cardiovascular disease." The EAG are not fully satisfied that the inclusion criteria were appropriate, as conditions classified as "severe or debilitating pulmonary disease" were not defined by the company.

Furthermore, the EAG asked the company to clarify whether there was a limit on the number of comorbidities or medications that a participant in ALPINE could have. The company responded that details were contained within the ALPINE CSR and provided this information in the reference pack.[12] Overall, the distribution of characteristics between the zanubrutinib and ibrutinib arms was generally well-balanced, though the company noted that there were small differences in sex and age (CS Section B.2b.3.4, p.79).[6]

The EAG asked the company to provide the average number of comorbidities participants in ALPINE had and how many medications on average they were taking. The company did not provide a mean estimate per arm in their response.[12] However, the company did state that one or more comorbidities were reported in [redacted] participants in the zanubrutinib arm and [redacted] participants in the ibrutinib arm.[12] Additionally, the company stated that almost all participants in the safety analysis set received at least one concomitant medication ([redacted] in the zanubrutinib arm and [redacted] in the ibrutinib arm), with the most common medications being antibacterial medications for systemic use, analgesics, antigout preparations and antivirals for systemic use.[12]

The company did not provide any information in the CS on the prior lines of treatment the study participants may have had. Clinical advice to the EAG suggested that prior treatments typically expected in patients with R/R CLL include: CIT (e.g. BR, chlorambucil plus Obinutuzumab, FCR); venetoclax monotherapy; VenO; or VenR. Additionally, the EAG's clinical advisor noted that small numbers of patients may have had allogeneic bone marrow transplant, or treatments with other novel agents not previously mentioned, in early phase trials.

As such, the EAG asked the company to provide the number and type of prior lines of therapy that participants had received previously. The company provided this information in their response to the clarification letter.[12] This has been presented previously in Table 3.14. Most participants only received one prior line of therapy before commencement of the study treatment. Furthermore, the company also provided the most reported prior lines of therapy received by the trial participants.[12] These included: FCR; venetoclax-based regimens (including VenR and VenO); chlorambucil-based regimens (including chlorambucil-obinutuzumab, chlorambucil-prednisone and chlorambucil-rituximab); and bendamustine-based regimens (including BR). Additionally, the company also provided the full list of other prior lines of therapy the trial participants received in the ALPINE CSR, provided in the reference pack.[12] Following clinical advice, the EAG were satisfied that this reflected the general characteristics of the population seen in clinical practice.

3.2.2.4 ALPINE efficacy

The efficacy outcomes of zanubrutinib in ALPINE of relevance to the decision problem and economic model of R/R CLL are shown in Table 3.17. Participants randomised to zanubrutinib and ibrutinib had a median follow-up of 24.34 and 23.82 months, respectively (CS Section B.2b.4.3, p.84).[6]

Table 3.17: Key efficacy outcomes in ALPINE

	Zanubrutinib (N=327)	Ibrutinib (N=325)
INV-assessed ORR (DCO 01 December 2021)		
Complete response, n (%)	[redacted]	[redacted]
Overall response rate, n (%) [95% CI]	[redacted]	[redacted]
Response ratio (95% CI) [p-value]	[redacted]	
IRC-assessed ORR (DCO 01 December 2021)		
Complete response, n (%)	[redacted]	[redacted]
Overall response rate, n (%) [95% CI]	[redacted]	[redacted]
Response ratio (95% CI) [p-value]	[redacted]	
INV-assessed PFS (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Events, HR (95% CI) [p-value]	[redacted]	
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
INV-assessed PFS (DCO 08 August 2022)		
Events, n (%)	87 (26.6)	118 (36.3)
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Events, HR (95% CI) [p-value]	0.65 (0.49, 0.86); p=0.0024	
Median (95% CI) [months]	NE (34.3, NE)	34.2 (33.3, NE)
IRC-assessed PFS (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Events, HR (95% CI) [p-value]	[redacted]	
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
IRC-assessed PFS (DCO 08 August 2022)		
Events, n (%)	88 (26.9)	120 (36.9)

Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Events, HR (95% CI) [p-value]	0.65 (0.49, 0.86); p=0.0024	
INV-assessed DOR (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Median, (95% CI)	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
IRC-assessed DOR (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Median, (95% CI)	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
TTTF (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
HR [95% CI]	[redacted]	
P-value	[redacted]	
Median follow-up, months (95% CI)	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
OS (DCO 01 December 2021)		
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
Source: CS, Table 35, Table 36, Table 38, Table 39, Table 40, Table 41[6]		

Abbreviations: CI = Confidence interval; CS = Company submission; DCO = Data cut-off; DOR = Duration of response; HR = Hazard ratio; INV = Investigator; IRC = Independent Review Committee; ORR = Overall response rate; OS = Overall survival; PD = Progressive disease; PFS = Progression-free survival; PR = Partial response; PRL = Partial response with lymphocytosis; SD = Stable disease; TTTF = Time to treatment failure.

The company performed exploratory sensitivity analyses on the primary endpoint of INV-assessed ORR for ALPINE, which included the assessment of PRL that were followed by PR or higher responses which, according to the company, confirmed the robustness of the primary analysis (CS Section B.2b.6.2).[6]

The company provided key efficacy outcomes for patients with R/R CLL from ALPINE based on the interim data-cut conducted on 01 December 2021. The company also provided within the clinical evidence late breaking data for PFS with a data cut-off point on 08 August 2022 (CS Section B.2b.6).[6] These data were not included in the economic model and the company stated "it is not expected to impact the cost-effectiveness estimates."[6]

The results of the ALPINE trial showed a statistically significant improvement in overall response for zanubrutinib compared with ibrutinib for the study's primary outcome, INV-assessed ORR ([redacted]) and IRC-assessed ORR ([redacted]). INV-assessed complete response rate was also higher in the zanubrutinib arm [redacted] than the ibrutinib arm [redacted].[6] Similar to ORR, zanubrutinib also demonstrated a statistically significant result of non-inferiority for INV- and IRC-accessed PFS, as well as TTTF. The company stated that TTTF was not reached for either zanubrutinib or ibrutinib at a median follow-up of 25.1 months in both arms. However, when compared to ibrutinib, treatment with zanubrutinib was associated with a statistically significant [redacted] reduction in TTTF [redacted]).[6]

Non-inferiority could not be established for OS and the company stated this may be due to immature data for a chronic illness such as CLL. The 95% CIs crossed the line of no effect ([redacted]) (CS Section B.2b.6.3, p. 95-7).[6] The CS states that the late breaking data from the data cut-off on 08 August 2022, and a lower HR with narrow confidence interval, demonstrated that the difference in number of deaths between zanubrutinib and ibrutinib further increased, therefore suggesting that a statistically significantly improvement in OS may be demonstrated with more mature data (CS Section B.2b.6.3, p. 96).[6]

EAG Comment: While superiority for zanubrutinib was established for PFS (INV-assessed: [redacted]; IRC-assessed: [redacted]) and ORR (INV-assessed: [redacted]; IRC-assessed: [redacted]), non-inferiority was not established for OS, a key efficacy outcome.

It was also unclear from the CS whether the sensitivity analyses for INV-assessed ORR and PFS in ALPINE were pre-planned within the protocol. As such, the EAG asked the company whether the sensitivity analyses were pre-planned or post-hoc analyses. The company provided these details within the ALPINE protocol, which was provided alongside the company's response to the clarification letter in the reference pack.[12] The EAG were satisfied that the sensitivity analyses were pre-planned within the protocol.

3.2.2.5 Participant-reported outcomes in ALPINE

The company reported that zanubrutinib showed greater improvements in HRQoL based on the mean changes in EORTC QLQ-C30 domain scores from baseline compared to ibrutinib. Pain was reported

as showing similar improvement across both trial arms (CS, Table 42).[6] The CS also states that the EQ-5D VAS showed a consistently better improvement in mean difference [SD] from baseline in patients in the zanubrutinib arm compared with patients in the ibrutinib arm at cycle 7 (zanubrutinib: [redacted]; ibrutinib: [redacted]) and cycle 13 (zanubrutinib: [redacted]; ibrutinib: [redacted]) (CS Section B.2b.6.3, p.98).[6]

EAG Comment: The EAG requested that the company provide mean EORTC QLQ-C30 scores from baseline, cycle 7 and cycle 13 in addition to the change scores presented in CS, Table 42.[6,12] The company responded with EORTC QLQ-C30 scores from baseline, cycle 7 and cycle 13, which are reported in Table 3.18.[12]

Table 3.18: Mean EORTC QLQ-C30 scores in ALPINE

PRO endpoint	Zanubrutinib			Ibrutinib		
	Baseline	Cycle 7[a]	Cycle 13[a]	Baseline	Cycle 7[a]	Cycle 13[a]
GHS/QoL	[redacted]					
Physical function	[redacted]					
Role function	[redacted]					
Fatigue	[redacted]					
Nausea/Vomiting	[redacted]					
Diarrhoea	[redacted]					
Pain	[redacted]					

Source: Company response to clarification letter[12]
[a] One cycle = 28 days
Note: Only patients with data at both baseline and each post-baseline visit were included in the summary statistics for change from baseline.
Abbreviations: GHS = Global health status; PRO = Patient-reported outcomes; SD = Standard deviation; QoL = Quality of life.

The EAG requested that the company provide the mean overall EORTC QLQ-C30 scores at each time point.[12] The company did not provide these scores and stated that, according to the EORTC QLQ-C30 Scoring Manual, "the use of a total, global score based upon the sum of all items is strongly cautioned against and the GSH/QoL scale should be used as the overall summary measure."[12,43] However, alongside the mean GHS/QoL scores, the company also presented additional scores for timepoints beyond cycle 13 in the CSR, which was included in the reference pack.[12]

The company stated that there were significant improvements in some EORTC QLQ-C30 domains when measured using mean change scores from baseline. However, the EAG has concerns relating to this estimation, as it was unclear to the EAG how the mean was estimated and whether the company controlled for potential baseline imbalances between zanubrutinib and ibrutinib.[6] It is unclear whether data are sufficiently precise to rule out clinically meaningful differences between groups as baseline data were not reported.

The EAG also requested that the company provide descriptive summaries (including mean and measure of variance) for the EQ-5D-5L utility data for each time-point. The company responded by providing EQ-5D-5L data for ALPINE at the 31 December 2020 data cut-off. The company provided data at baseline, between cycle 4 and cycle 28, end of treatment, and the long-term follow-up at 1 and 3 months.[12] These data are discussed in further detail in Section 4.4.8.

The EAG cannot comment on the EQ-5D VAS scores presented, as the company only narratively reported on mean improvements in the EQ-5D VAS at cycle 7 and cycle 13 (CS Section B.2b.6.3, p. 98).[6]

3.2.2.6 Adverse events in ALPINE

The company used Grade 3 or higher TEAEs or post-treatment AEs reported in ≥ 1% of participants in ALPINE, as shown in Table 3.19, to inform the economic model (Section 4.4.8).[6]

Table 3.19: Grade 3 or higher treatment-emergent and post-treatment adverse events reported in ≥1% of participants in ALPINE

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One Grade 3 or Higher TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders		
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cardiac disorders		
Atrial fibrillation	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	[redacted]	[redacted]
General disorders and administration site conditions		
Pyrexia	[redacted]	[redacted]
Infections and infestations		
Pneumonia	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Sepsis	[redacted]	[redacted]
Investigations		
Neutrophil count decreased	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Metabolism and nutrition disorders		
Diabetes mellitus	[redacted]	[redacted]
Nervous system disorders		
Syncope	[redacted]	[redacted]
Renal and urinary disorders		
Acute kidney injury	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]

Source: CS, Table 65[6]
Abbreviations: AE = Adverse event; CS = Company submission; TEAE = Treatment-emergent adverse event.

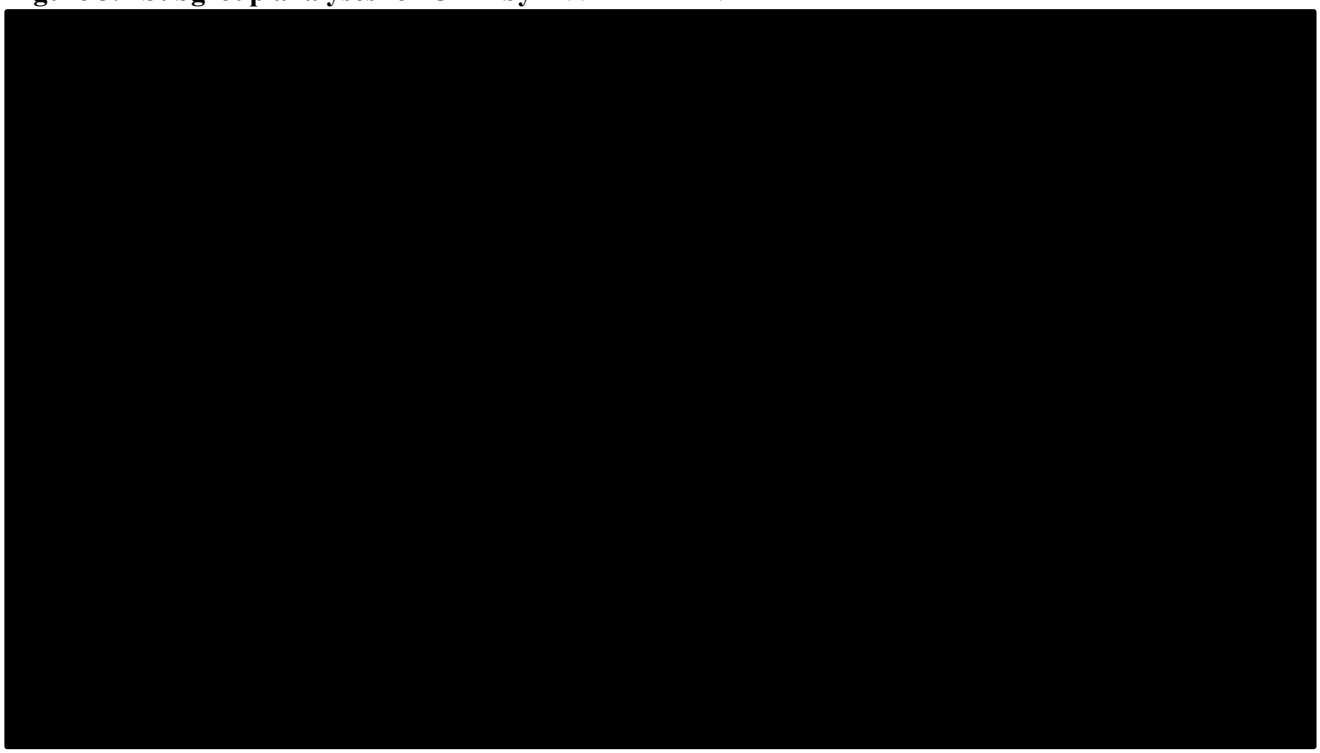
The company state that eight participants (2.4%) in the zanubrutinib arm discontinued treatment due to COVID-19 related AEs (CS Section B.2b.4.3, p.84).[6] Fatality was observed in all of the COVID-19-related AEs (CS Section B.2b.4.3, p.84).[6] Participants discontinued study treatment due to AEs in the zanubrutinib arm 45 (13.8%) and the ibrutinib 59 (18.2%). Study treatment was also discontinued due to progressive disease 13 (4%) in the zanubrutinib arm and the ibrutinib arm 32 (9.8%) (CS Section B.2b.4.3, p.84).[6]

EAG Comment: As previously mentioned in Section 3.2.1.6, the EAG asked the company to provide clarification on the discrepancy in the proportion of reported AEs in participants with R/R CLL. The company responded that the R/R population were more likely to suffer from AEs, so a lower limit of 2% proportion experiencing Grade 3 or more TEAEs was placed on this population.[12] The EAG have identified a discrepancy in the reporting of the Grade 3 or higher TEAEs. In the clinical effectiveness section, Grade 3 or higher TEAEs or post-treatment AEs reported in ≥ 1% of participants in ALPINE was reported (CS Table 65).[6] However, in the economic model Grade 3 or more TEAEs occurring in ≥ 2% of patients by treatment was used (CS Table 109).[6] It is unclear to the EAG, both from the CS and the company's response to the clarification letter, why this discrepancy exists.

3.2.2.7 Subgroup analyses in ALPINE

The company presented subgroup analyses on INV-assessed ORR and PFS in CS Section B.2b.7 (p. 98-101).[6] Compared with ibrutinib, the results showed a statistically significant improvement in ORR in patients in the zanubrutinib arm with unmutated IGHV (rate difference: [redacted]), and patients with del17p or TP53 mutation status (rate difference: [redacted]). The company also noted that the late breaking data from the 8 August 2022 data cut-off showed statistically significant improvement in the subgroup analyses performed in patients aged ≥ 65 years, without del17p or TP53 mutation status, without bulky disease, and Binet stage C, when previously only a numerical improvement had been demonstrated (CS Section B.2b.7, p. 98).[6] Subgroup analysis on INV-assessed PFS also demonstrated a statistically significant improvement in PFS with zanubrutinib in comparison to ibrutinib in patients with unmutated IGHV ([redacted]), and patients with del17p or TP53 mutation status ([redacted]) (CS Section B.2b.7, p. 99-100).[6] Full subgroup analyses as presented in the CS are detailed in Figures 3.2 and 3.3.

Figure 3.2 Subgroup analyses for ORR by INV in ALPINE



Source: CS, Figure 19[6]

[a] Rate difference (zanubrutinib minus ibrutinib) and 95% confidence interval were unstratified for subgroups.

[b] Bulky disease of yes is derived from any target lesion longest diameter ≥ 5 cm.

Abbreviations: CLL = Chronic lymphocytic leukaemia; CS = Company submission; ECOG = Eastern Cooperative Oncology Group; IgVH = Immunoglobulin heavy chain gene; ORR = Overall response rate; PS = Performance status; PFS = Progression-free survival; IRC = Independent review committee; LDH = Lactate dehydrogenase; LDi = Longest diameter; SLL = Small lymphocytic lymphoma; TP53 = Tumour protein P55; ULN = Upper limit of normal; VAF = Variant allele frequency.

Figure 3.3 Subgroup analyses for PFS by INV in ALPINE

Source: CS, Figure 19[6]
[a] Hazard ratio and 95% CI were from a Cox regression model with the ibrutinib arm as the reference group. Estimates were unstratified for subgroups.
[b] Bulky disease of yes is derived from any target lesion longest diameter ≥ 5 cm
Abbreviations: CLL = Chronic lymphocytic leukaemia; CS = Company submission; ECOG = Eastern Cooperative Oncology Group; IgVH = Immunoglobulin heavy chain gene; PS = Performance status; PFS = Progression-free survival; IRC = Independent review committee; LDH = Lactate dehydrogenase; LDi = Longest diameter; SLL = Small lymphocytic lymphoma; TP53 = Tumour protein P55; ULN = Upper limit of normal; VAF = Variant allele frequency.

EAG Comment: The CS states a subgroup analysis would be conducted for patients with positive hepatitis B core antibody (HBcAB).[6] The time from initial diagnosis to randomisation and disease type are listed as pre-specified subgroups for ALPINE in Table 29 of the CS but were not reported in Section B.2b.7.[6] The EAG requested that the company provide the subgroup analyses for this patient population for both INV-assessed ORR and PFS.[12] The company responded that these were described in the clinical trial protocol and SAP for ALPINE, which were provided to the EAG.[12,45,46] Although the SAP was provided,

[redacted].[12,45] The EAG cannot comment further, as it is uncertain whether or not a subgroup analysis was conducted for patients with positive HBcAB.[redacted].[12,45] As such, it is also unclear to the EAG whether this is a plausible source of bias.

The CS also listed the del17p status and TP53 mutation status as separate subgroups within the study design (CS, Table 29).[6] However, both statuses were combined in the subgroup analysis reported in the CS (Figure 19).[6] The EAG queried the rationale for combining both statuses and asked the company to provide separate subgroup analyses for del17p status and TP53 mutation for ALPINE. The SAP provided by the company stated: "[redacted]."[12,45,47] The sample size for participants with del17p status and TP53 mutations was small and, as such, the EAG are satisfied with the rationale of combining both subgroups.

Furthermore, the EAG noted that the CS presented prior lines of therapy as a subgroup analysis (CS, Figure 19) but this was not previously stated as a prespecified subgroup in Table 29 of the CS.[6] The EAG asked the company for clarification on whether the subgroup analysis for prior lines of therapy was added post-hoc and to provide a rationale for including this subgroup. The company responded that the prespecified subgroups were detailed in the SAP and the clinical trial protocol for ALPINE which were provided to the EAG.[12,45,46] The EAG identified a discrepancy in reporting of this subgroup across the CS. The prior lines of therapy were reported in Figure 19 in the CS [redacted] whereas, this subgroup was not included in CS Table 29.[12,45] It is unclear to the EAG, both from the CS and the company's response to the clarification letter, why this discrepancy exists.

3.3 Critique of trials identified and included in the indirect comparison and/or matching adjusted indirect comparison (MAIC)

In the absence of head-to-head trial evidence for the NICE scope comparisons involving zanubrutinib, acalabrutinib or ibrutinib (in previously untreated patients with CLL), or zanubrutinib with acalabrutinib (in patients with R/R CLL), the company conducted ITCs in the form of MAICs.

All efficacy and safety data relevant to patients with untreated CLL were provided from two relevant RCTs: ELEVATE-TN for acalabrutinib;[34] and SEQUOIA for zanubrutinib and BR.[29] In addition, all efficacy and safety data relevant to patients with R/R CLL were provided from three relevant RCTs: ASCEND and ELEVATE-RR for acalabrutinib;[35,36] and ALPINE for zanubrutinib and ibrutinib.[30] Table 3.20 presents a brief description of the populations in each of the trials included in the CS.

Table 3.20: Summary of the populations of the comparisons included in the company submission

Trial name	Population	Sample size	17p deletion and/or TP53 mutation	Comparison
Analyses for untreated CLL population				
SEQUOIA[29]	Untreated CLL with and without del17p and/or	Acalabrutinib: n=179;	Combined Cohort 1 (without del17p and/or TP53	Zanubrutinib versus acalabrutinib (unanchored MAIC)

	TP53 mutation	Zanubrutinib: Model 1: ESS=107.5 Model 2: ESS=124.5	mutation) and Cohort 2 (del17p and/or TP53 mutation) 37% (but reduced to 12.8% after matching in MAIC in both models).	
ELEVATE-TN[34]	Untreated CLL		87.2% without del17p and/or TP53 12.8% with del17pand/or TP53	
ALPINE[30]	R/R CLL (proxy for untreated CLL)	Zanubrutinib: n=327 Ibrutinib: n=325	Patients with del17p and/or TP53 mutation was 22.9% in zanubrutinib arm and 23.1% in ibrutinib arm.	Zanubrutinib versus ibrutinib (direct evidence from ALPINE[30])
SEQUOIA[29]	Untreated CLL	Zanubrutinib: n=111	100% patients with del17p and/or TP53 mutation (Cohort 2)	Zanubrutinib versus ibrutinib in untreated CLL (naïve comparison)
Mato 2018[5]	Untreated CLL	Ibrutinib n=391	43% with del17p and/or TP53 mutation	
Analyses for R/R population				
ALPINE[30]	R/R CLL	Acalabrutinib: n=268 Ibrutinib: n=265; Model 1: ESS: n=63; Model 2: ESS: n=79; Zanubrutinib: Model 1: ESS=79 Model 2: ESS=87	Acalabrutinib: Total arm: 45.3% of patients had a del17p mutation and 37.4% of patients had a TP53 mutation. Ibrutinib: Total arm: 45.3% of patients had a del17p mutation and 42.3% of patients had a TP53 mutation. Model 1: 45.3% of patients had a del17p mutation and 42.3% of patients had a TP53 mutation. Model 2: 45.3% of patients had a del17p mutation and 24.7%	Zanubrutinib versus acalabrutinib in R/R CLL (anchored MAIC – ibrutinib common comparator)
ELEVATE-RR[36]	R/R CLL			

			of patients had a TP53 mutation. Zanubrutinib: 45.3% of patients had a del17p mutation and 37.4% of patients had a TP53 mutation in both models.	
ALPINE[30]	R/R CLL	Acalabrutinib: n=155 Zanubrutinib: Model 1: ESS=143 Model 2: ESS=103	All: 18.1% of patients had a del17p mutation and 25.2% of patients had a TP53	Zanubrutinib versus acalabrutinib in R/R CLL (unanchored MAIC)
ASCEND[35]	R/R CLL			

Source: adapted from CS, Tables 13,32,43,47,50,52,53,56,58[6]
Abbreviations: BR = Bendamustine-rituximab; CLL = Chronic lymphocytic leukaemia; del17p = 17p deletion; MAIC = Matching-adjusted indirect comparison; R/R = Relapsed or refractory.

EAG comment: As noted in Section 2.3, the EAG disagrees with the company's decision not to include trials on the effectiveness of VenR in patients with R/R CLL as a comparator for zanubrutinib. The EAG also considered VenO as a potential comparator for zanubrutinib in participants with untreated CLL and del17p or TP53 mutation, or in participants where FCR or BR are unsuitable. The comparative effectiveness of these interventions is explored in EAG analyses (see Section 3.5).

The EAG accept concerns raised by the company in the CS regarding significant heterogeneity in the design and selection of comparators in CLL trials and agree that the underlying assumption of an NMA would not be valid.[6] Therefore, the EAG agree it was appropriate to conduct MAICs for the comparators considered in the CS.[6]

3.3.1 Indirect comparison for previously untreated CLL

The indirect comparison for the previously untreated CLL population is discussed in Section 3.3.1 and the indirect comparison for the R/R CLL population is discussed in Section 3.3.2.

3.3.1.1 Baseline characteristics

The trial characteristics and eligibility criteria for the two studies included in the MAIC analysis (SEQUOIA[29], ELEVATE-TN,[34]) is provided in Table 44 in the CS.[16] The company also reported an additional study[5] that included a comparison with ibrutinib to supplement the results of the MAICs (see Section 3.3.1.5).

3.3.1.2 Study characteristics and demographics

The trial characteristics and eligibility criteria for SEQUOIA[29] and ELEVATE-TN[34] are provided in Tables 44 and 45 in the CS.[6] The median follow-up was 28.3 months in ELEVATE-TN,[34] compared with 26.35 months in SEQUOIA.[29]

IPD from the SEQUOIA trial was included in the MAIC.[29] As baseline characteristics were not reported separately for patients with del17p mutation and patients without del17p from ELEVATE-TN,[34] it was not possible to conduct separate analyses using the populations in Cohort 1 (arm A) and Cohort 2 (arm C) of SEQUOIA.[29] As such, data for zanubrutinib from Cohort 1 (arm A) and Cohort 2 (arm C) of SEQUOIA were pooled in order to create a cohort that included patients with and without del17p to match the eligibility criteria for ELEVATE-TN.[29,34]

The pooled trial population was adjusted to match the average baseline characteristics reported in ELEVATE-TN for participants receiving acalabrutinib.[34] The unadjusted population characteristics of the acalabrutinib monotherapy arm in ELEVATE-TN and pooled zanubrutinib population from SEQUOIA were presented in Table 45 in the CS.[6,29,34]

EAG comment: The two trials that form the MAIC analysis reported reasonably similar important baseline characteristics such as age, sex and ethnicity. While some baseline variables such as mutation status slightly differed (33.5 to 43.6%), the EAG do not have any major concerns.

3.3.1.3 Prognostic factors included in the MAIC

A comprehensive list of prognostic factors were considered in the MAIC analysis.[6] The population characteristics included in the MAIC are presented in Table 3.21. Two matching models were considered in the analyses.

Table 3.21: Matching models for pooled zanubrutinib populations in SEQUOIA versus acalabrutinib monotherapy population in ELEVATE-TN

Population Characteristics		Model 1	Model 2
IGHV mutation	Unmutated (versus mutated), %	✓	✓
17p deletion and/or TP53 mutation	del17p only (versus no del17p and no TP53 mutation), %	✓	✓
	del17p and TP53 mutation (versus no del17p and no TP53 mutation), %	✓	✓
	TP53 mutation only (versus no del17p and no TP53 mutation), %	✓	✓
11q deletion	Yes (versus no), %	✓	✓
β2-Microglobulin, mg/L	> 3.5 (versus ≤ 3.5), %	✓	✓
Bulky disease, LDi in cm	≥ 5 (versus < 5), %	✓	✓
Age, years	≥ 75 (versus < 65), %	✓	✓
	≥ 65 and < 75 (versus < 65), %	✓	✓

Population Characteristics		Model 1	Model 2
	Median	-	-
Geographic Region	North America or Europe (versus others), %	✓	✓
Sex	Male (versus female)	✓	✓
Complex karyotype (≥3 abnormalities)	Yes (versus no)	-	-
ECOG PS	1 (versus 2), %	✓	✓
Cancer type	CLL (versus SLL)	✓	✓
Time from initial diagnosis	Median	✓	✓
Ethnicity	Hispanic or Latino (versus other), %	✓	-
Creatinine clearance, mL/min	< 60 (versus ≥ 60), %	✓	✓
	Median	-	-
Any cytopenia	Yes (versus no), %	-	-
Anaemia	Yes (versus no), %	-	-
Thrombocytopenia	Yes (versus no), %	-	-
Neutropenia	Yes (versus no), %	-	-
CLL-IPI	High or very high (versus low or intermediate), %	✓	✓
Rai Stage	II (versu I), %	✓	✓
	III (versus I), %	✓	✓
	IV (versus I), %	✓	✓

Source: CS, Table 46[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CLL-IPI = Chronic lymphocytic leukaemia international prognostic index; CIRS = Cumulative Illness Rating Scale; ECOG = Eastern Cooperative Oncology Group Performance Status Scale; ESS = Effective sample size; IGHV = immunoglobulin heavy chain gene; LDi = Longest diameter; PS = Performance status; SLL = Small lymphocytic lymphoma; TN = Treatment-naïve; TP53 = Tumour protein P53 gene.

The company excluded complex karyotype as a potential covariate in the list of matching factors in the model as it had a high missing rate in the SEQUOIA trial (approximately 47%).[29] [redacted][8]

[redacted][8]

EAG comment: The EAG have no concerns about the prognostic factors considered by the company. The clinical advisor to the EAG confirmed that these factors were comprehensive. Model 1 additionally adjusted for ethnicity, otherwise all other prognostic factors were identical in both models. The EAG accept that ethnicity is an important baseline characteristic. However, the company did not justify the specific dichotomy of Hispanic/Latino versus other.

The EAG's main concern surrounds the additional uncertainty associated with an unanchored MAIC, as the potential impact of unknown confounders is greater for these analyses.[48] Furthermore, an unanchored MAIC analysis compromises the benefits of randomisation (theoretically balancing all known and unknown prognostic factors across groups) in the original RCTs. However, the EAG accept that this uncertainty is unavoidable, as ELEVATE-TN and SEQUOIA did not contain a common comparator arm.[29,34] The unanchored MAIC conducted adequately followed NICE DSU guidelines, as described in CS Section B.2.9.1.1 (p.105) and Appendix N.[6,49]

The EAG would have preferred the company to have explored complex karyotype in sensitivity analyses to assess that their assumption was valid. However, due to the nature of loss of data and a reduction in ESS in a MAIC when there are substantial missing data in matching variables, the EAG accept the decision made on this basis.

The EAG also question whether the ESS was "sufficiently high" with the aim of detecting any true differences between treatments that may or may not be present (CS Section B.2.9.1.1).[6] The company did not provide sufficient information or provide any justification for their assessment that the ESS was "sufficiently high."

3.3.1.4 Outcomes

As the primary endpoint reported in both SEQUOIA and ELEVATE-TN was IRC-assessed PFS,[6,29,34] analyses were conducted in the MAIC using this outcome, as well as OS. For these time-to-event outcomes, the adjusted KM curves were estimated in the CS by a weighted KM analysis and plotted alongside the KM curves of the unadjusted population and the corresponding population in the comparator study to illustrate the direction and magnitude of the shift due to the adjustment (CS Section B.2.9.1.1).[6]

To estimate the relative treatment effect on the time-to-event efficacy outcomes between zanubrutinib and acalabrutinib, IPD from the SEQUOIA were combined with the restructured IPD of ELEVATE-TN (CS Section B.2.9.1.1, p.111).[6,29,34] A Cox proportional hazard regression model was then fitted using the treatment indicator as a predictor to derive naïve estimates of comparative efficacy before population adjustment. The company then fitted a weighted Cox proportional hazard regression model to derive estimates of comparative effect after population adjustment. HRs along with 95% CIs were reported for both the unweighted and weighted Cox proportional regression models to provide naïve and MAIC-adjusted estimates of the relative efficacy (CS Section B.2.9.1.1).[6]

EAG comment: The EAG do not have any concerns with the methodological conduct or outcomes reported.

3.3.1.5 Results

A summary of the population characteristics after matching by weights generated from both Model 1 and Model 2 are presented in Table 3.22. After matching, all matched baseline characteristics were balanced (i.e. sufficiently similar) between the trials, as demonstrated in the histograms of normalised weights presented in Figures 3.4 and 3.5 for Model 1 and Model 2, respectively.[6]

Table 3.22: Population characteristics of the acalabrutinib monotherapy population in the ELEVATE-TN study vs. zanubrutinib population in the SEQUOIA after matching

Population characteristics		**Acalabrutinib (N = 179)**	**Zanubrutinib Model 1 (ESS = 107.5)**	**Zanubrutinib Model 2 (ESS = 124.5)**
IGHV mutation	Unmutated (versus mutated), %	33.50%	[redacted]	[redacted]
17p deletion and/or TP53 mutation	del17p only (versus no del17p and no TP53 mutation), %	2.20%	[redacted]	[redacted]
	del17p and TP53 mutation (versus no del17p and no TP53 mutation), %	6.70%	[redacted]	[redacted]
	TP53 mutation only (versus no del17p and no TP53 mutation), %	3.90%	[redacted]	[redacted]
11q deletion	Yes (versus no), %	17.30%	[redacted]	[redacted]
β2-Microglobulin, mg/L	> 3.5 (versus ≤ 3.5), %	78.20%	[redacted]	[redacted]
Bulky disease, LDi in cm	≥ 5 (versus < 5), %	38.00%	[redacted]	[redacted]
Age, years	≥ 75 (versus < 65), %	27.90%	[redacted]	[redacted]
	≥ 65 and < 75 (versus < 65), %	56.40%	[redacted]	[redacted]
	Median	70.00	[redacted]	[redacted]
Region	North America or Europe (versus others), %	88.30%	[redacted]	[redacted]
Sex	Male (versus female), %	62.00%	[redacted]	[redacted]
Complex karyotype (≥3 abnormalities)	Yes (versus no), %	17.30%	[redacted]	[redacted]
ECOG PS	1 (versus 2), %	92.20%	[redacted]	[redacted]
Cancer type	CLL (versus SLL), %	100.00%	[redacted]	[redacted]
Time from initial diagnosis	Median, months	24.40	[redacted]	[redacted]
Ethnicity	Hispanic or Latino (versus other), %	6.60%	[redacted]	[redacted]
Creatinine clearance, mL/min	< 60 (versus ≥ 60), %	26.80%	[redacted]	[redacted]
	Median	75.00	[redacted]	[redacted]
Any cytopenia	Yes (versus no), %	47.50%	[redacted]	[redacted]

Population characteristics		Acalabrutinib (N = 179)	Zanubrutinib Model 1 (ESS = 107.5)	Zanubrutinib Model 2 (ESS = 124.5)
Anaemia	Yes (versus no), %	38.00%	[redacted]	[redacted]
Thrombocytopenia	Yes (versus no), %	18.40%	[redacted]	[redacted]
Neutropenia	Yes (versus no), %	5.60%	[redacted]	[redacted]
CLL-IPI	High or very high (versus low or intermediate), %	87.50%	[redacted]	[redacted]
Rai stage	II (versus I), %	24.60%	[redacted]	[redacted]
	III (versus I), %	27.90%	[redacted]	[redacted]
	IV (versus I), %	20.70%	[redacted]	[redacted]

Source: CS, Table 47[6]

Abbreviations: CLL = Chronic lymphocytic leukaemia; CLL-IPI = Chronic lymphocytic leukaemia international prognostic index; CIRS = Cumulative Illness Rating Scale; ECOG =Eastern Cooperative Oncology Group Performance Status Scale; ESS = Effective sample size; IGHV = immunoglobulin heavy chain gene; PS –Performance status; SLL = Small lymphocytic lymphoma; TN = Treatment-naïve; TP53 = Tumour protein P53 gene.

Figure 3.4: Distribution of the normalised weights for MAIC comparing SEQUOIA and ELEVATE-TN – Model 1

Source: CS, Figure 21[6]
Abbreviations: ESS = Effective sample size; MAIC = Matching-adjusted indirect comparison.

Figure 3.5: Distribution of the normalised weights for MAIC comparing SEQUOIA and ELEVATE-TN – Model 2

Source: CS, Figure 22[6]
Abbreviations: ESS = Effective sample size; MAIC = Matching-adjusted indirect comparison.

The MAIC results for IRC-assessed PFS and OS both before and after matching are summarised in Table 3.23.[6] In Model 1, there was no statistically significant difference in IRC-assessed PFS between zanubrutinib and acalabrutinib (HR [redacted], 95% CI [redacted]). Similarly, there was no statistically significant difference in OS between zanubrutinib and acalabrutinib (HR [redacted], 95% CI [redacted]). The results of Model 2 were consistent with Model 1, demonstrating no statistically significant difference between zanubrutinib and acalabrutinib in IRC-assessed PFS (HR [redacted], 95% CI [redacted]) or OS (HR [redacted], 95% CI [redacted]) (CS Section B.2.9.1.2).[6]

Table 3.23: Summary of MAIC results for zanubrutinib versus acalabrutinib for patients with untreated CLL

	PFS (IRC)		OS	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 48[6]
Abbreviations: Cl = Confidence interval; CLL = Chronic lymphocytic leukaemia; HR = Hazard ratio; IRC = Independent review committee; MAIC = Matching-adjusted indirect comparison; OS = Overall survival; PFS = Progression-free survival.

The KM curves for IRC-assessed PFS for acalabrutinib and zanubrutinib (both pre- and post-adjustment) are presented for Model 1 and Model 2 in Figures 3.6 and 3.7.[6] There is little change in the pre-matching and post-matching KMs for zanubrutinib, suggesting that the populations in ELEVATE-TN and SEQUOIA were relatively well-balanced.[29,34]

Figure 3.6: KM Analysis of PFS-IRC for MAIC comparing SEQUOIA and ELEVATE-TN – Model 1

Source: CS, Figure 23[6]
Abbreviations: IRC = Independent review committee; KM = Kaplan-Meier; MAIC = Matching-adjusted indirect comparison; PFS = Progression free survival.

Figure 3.7: KM Analysis of PFS-IRC for MAIC comparing SEQUOIA and ELEVATE-TN – Model 2

Source: CS, Figure 24[6]
Abbreviations: IRC = Independent review committee; KM = Kaplan-Meier; MAIC = Matching-adjusted indirect comparison; PFS = Progression free survival.

The company state that the MAIC demonstrates that zanubrutinib is at least non-inferior to acalabrutinib in previously untreated adults with CLL who are unsuitable for FCR and BR therapy ("unfit"), in participants both with and without del17p or TP53 mutation ("high-risk"), although there were very few participants with these present in the MAIC (CS Section B.2.9.1.2, p.116).[6]

[redacted]

[8]

The company also reported an additional study that included a comparison with ibrutinib as alluded to in Section 3.3.1.1. This was a naïve comparison assessing the efficacy of zanubrutinib with ibrutinib in patients with untreated CLL. Clinical efficacy for patients with 17p deletion treated with ibrutinib was extracted from Mato *et al*., (2018)[5] and compared with Cohort 2 (arm C) of SEQUOIA.[89] Mato *et al*., (2018)[5] was a retrospective study identified within the clinical SLR which presented data on patients who did not meet the inclusion criteria for the RESONATE-2 study (specifically <65 years and/or those with 17p deletion).

A formal MAIC was not conducted given that baseline characteristics for patients with a 17p deletion only, to align with the SEQUOIA eligibility criteria of Cohort 2 (arm C), were not published in Mato *et al*., (2018).[5] Instead, an unstratified Cox regression model was used to estimate HRs for PFS and OS. Based on this naïve comparison, there was no statistically significant difference in PFS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted]). However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted]).

EAG comment: The EAG note that the correct interpretation was applied in the CS (Section B.2.9.1.2) to the results shown in Table 3.23 but this is later confused with non-inferiority in the CS.[6,50] The 95% CI indicates the lower limit is consistent with zanubrutinib being associated with reduced PFS compared with acalabrutinib. Clinical advice to the EAG suggested these differences were clinically meaningful ([redacted]).
Therefore, these data are insufficient to conclude that zanubrutinib is non-inferior to acalabrutinib for IRC-assessed PFS.[50]

The EAG agrees the CS reported an appropriate assessment of the proportional hazards (PH) assumption for IRC-assessed PFS after population adjustment in both Model 1 and Model 2 in the CS.[6] The EAG accepts the company's conclusion that there was no evidence to doubt the PH assumption.

The EAG acknowledge that the company conducted a naïve comparison using data from Mato *et al*., (2018)[5] to complement the MAICs and to provide supportive data for the previously untreated "high-risk" population, but note that the study was retrospective, and at risk of potential confounding bias as factors such as age and IGHV mutation were not controlled for in the comparison.[20].

3.3.2 Indirect comparison for R/R in CLL

3.3.2.1 Baseline characteristics

The study characteristics and eligibility criteria for the three studies included in MAIC analyses (ALPINE, ELEVATE-RR and ASCEND) are provided in the CS (Tables 49 and 55).[16,30,35,36]

3.3.2.2 Study characteristics and demographics

The study characteristics and eligibility criteria of the trials used in the MAICs in the R/R CLL population are provided in the CS Tables 49 and 50 for ALPINE versus ELEVATE-RR and in CS Tables 55 and 56 for ALPINE versus ASCEND.[6,30,35,36] The median follow-up was 40.9 months in ELEVATE-RR, 24.3 months in ALPINE and 16.1 months in the ASCEND.[30,35,36] Since ELEVATE-RR only randomised participants with del17p or 11q deletion, the ITT population in ALPINE was restricted to the subset of high-risk participants to ensure comparability across populations.[30,36] The MAIC approach then used IPD from ALPINE and adjusted the trial population to match the average baseline characteristics of the acalabrutinib arm in ELEVATE-RR and ASCEND in separate comparisons.[30,35,36] The unadjusted population characteristics of the acalabrutinib monotherapy arms in ELEVATE-RR and ASCEND compared with the population in the zanubrutinib arm in ALPINE are presented in CS Tables 50 and 56, respectively.[6,30,35,36]

EAG comment: The EAG do not have any concerns about the approaches used. However, there is potentially important confounding in terms of differences in median follow-up between trials. The MAIC is unable to adjust for these differences.

As a consequence of the company excluding VenR and VenO as relevant comparators in the submission,[6,16] as previously discussed these treatments were not included as a comparator in any of the

MAIC analyses (see Sections 2.3 and 3.1.2). The EAG reaffirms that they did not agree with the exclusion of VenR and VenO as potential comparators (see Section 3.5).

3.3.2.3 Prognostic factors included in the MAIC

3.3.2.3.1 Indirect comparison for zanubrutinib versus acalabrutinib using ALPINE and ELEVATE-RR in R/R CLL

ELEVATE-RR and ALPINE contained a common comparator arm (ibrutinib).[30,36] Therefore, an anchored MAIC was conducted following the NICE DSU guidelines and methodology as outlined previously.[48] Full details of the prognostic factors and methodology are provided in the CS and CS Appendix N.[6,49]

A matching model including all mutually available covariates with prognostic or effect modifying potential was explored in the CS but led to an insufficiently low ESS (ESS = 31 for the zanubrutinib arm and ESS = 25 in the ibrutinib arm).[6] As such, to increase ESS the company used a matching model that only included covariates considered effect modifiers was fitted and prognostic factors with effect modifying potential (age, sex, bulky disease, complex karyotype and ECOG performance score) were excluded from the list of matching factors. The determination of covariates as effect modifiers was based on internal clinical consultation and the choice of covariates included within the models was validated at an advisory board conducted by the company on 03 November 2022.[8]

The population characteristics included in the MAIC are presented in Table 3.24.[6] Since there was a large imbalance in the proportion of participants with TP53 mutation (where the difference in del17p and del11q did not greatly differ) across the populations in ELEVATE-RR and ALPINE, the impact of excluding the variable was explored in Model 2, as shown in Table 3.24.[6,30,36]

Table 3.24: Matching parameters for ALPINE vs. ELEVATE-RR

Population characteristics		Model 1	Model 2
IGHV mutation	Mutated (versus unmutated), %	✓	✓
Cytogenetic mutation subgroups	Del17p, %	✓	✓
	Del11q, %	✓	✓
	TP53 mutation, %	✓	-
Complex karyotype (≥3 abnormalities)	Yes (versus no), %	-	-
β2-microglobulin, mg/L	> 3.5 (versus ≤ 3.5), %	✓	✓
Number of prior therapies	≥ 4 (versus 1–3), %	✓	✓
Bulky disease, LDi in cm	≥ 5 (versus < 5), %	-	-
Age, years	≥ 75 (versus < 75), %	-	-
	Median	-	-
Sex	Male (versus female), %	-	-
Cancer type	CLL (versus SLL)	✓	✓

Population characteristics		Model 1	Model 2
ECOG PS	2 (versus 0-1), %	-	-
Binet stage (CLL patients only)	A (versus C), %	✓	✓
	B (versus C), %	✓	✓

Source: CS, Table 51[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; del11q/del13q = Deletion of the long arm of chromosome 11/13; del17p = deletion of the short arm of chromosome 17; ECOG = Eastern Cooperative Oncology Group; IGHV = Immunoglobulin heavy chain gene; LDi = Longest diameter; PS = Performance status; R/R = Relapsed or refractory; SLL = Small lymphocytic lymphoma; TP53 = Tumour protein 53 gene.

[redacted]

EAG comment: The EAG shares the same generic concerns about the conduct of the MAIC as was outlined for the untreated CLL population in Section 3.3.1.2. The EAG has no criticisms of the approach and the selection of prognostic factors considered was comprehensive but, again, this comes with the caveat regarding the impact of potential unknown confounders.

The EAG note there is a trade-off between maximising the ESS and ensuring that important prognostic factors are included in the matching process to minimise potential biases and confounding. The company have attempted to fit the best models but, ultimately, data in the trials are too sparse to adequately achieve these given issues with missing data for some important prognostic factors. While the models may be valid, the EAG disagrees that the ESS is likely to be sufficient at detecting any differences in outcome that may or may not be present. The company do not provide justification for an ESS that would be sufficient to test the non-inferiority of zanubrutinib compared with acalabrutinib.[50]

3.3.2.3.2 Indirect comparison for zanubrutinib versus acalabrutinib using ALPINE and ASCEND in R/R CLL

As ASCEND and ALPINE did not contain a common comparator arm, an unanchored MAIC was conducted by the company that followed the NICE DSU guidelines and methodology, as described in CS Section B.2.9.3.1 (p.131) and in CS Appendix N.[6,30,35,49]

A matching model including all mutually available covariates with prognostic or effect modifying potential is shown in Table 3.25. To increase ESS, a matching model including only covariates considered effect modifiers was fitted and prognostic factors with effect modifying potential (age, sex, bulky disease, geographical region, ECOG performance score) were excluded from the list of matching factors in the CS.[6] The determination of covariates as effect modifiers in the CS was again based on internal clinical consultation and discussion with UK clinical experts in attendance at an advisory board conducted by the company on 03 November 2022.[8] As adjusting for covariates with either prognostic or effect modifying potential (Model 2) or effect modifying potential alone (Model 1) did not have a large impact on sample size, the impact of the additional adjustment was explored by the company.[6]

Table 3.25: Matching parameters for ALPINE versus ASCEND

Population characteristics	Model 1	Model 2

IGHV mutation	Unmutated (versus mutated), %	✓	✓
Cytogenetic mutation subgroups	Del17p, %	✓	✓
	Del11q, %	✓	✓
	TP53 Mutation, %	✓	✓
Number of prior therapies	2, %	✓	✓
	3, %	✓	✓
	≥ 4, %	✓	✓
Bulky disease	LDi in cm, 5 (versus < 5)	-	✓
Age	75 (versus < 75)	-	✓
Sex	Male (versus female), %	-	✓
Geographic region	US and Canada (versus Europe)	-	✓
	Australia and New Zealand (versus Europe)	-	✓
	Asia (versus Europe)	-	✓
Rai stage III-IV	(versus 0-II), %	✓	✓
ECOG performance status	2 (versus 0-1), %	-	-
Prior therapy	Purine analogue, %	-	-
	Anti-CD20 antibody, %	-	-
	Alkylators other than bendamustine, %	-	-
	Bendamustine, %	-	-

Source: CS, Table 57[6]
Abbreviations: ECOG = European Cooperative Oncology Group; IGHV = immunoglobulin heavy chain gene; LDi = Longest diameter.

EAG comment: The EAG express the same concerns about the unanchored nature of the analysis as outlined in Section 3.3.1.2 but had no other concerns about the conduct of the methodology.

3.3.2.4 Outcomes

3.3.2.4.1 Indirect comparison for zanubrutinib versus acalabrutinib using ALPINE and ELEVATE-RR in R/R CLL

In addition to the population characteristics extracted from ELEVATE-RR,[36] patient-level survival data (i.e. PFS and OS) were reconstructed from the published KM curves of ELEVATE-RR in the CS using NICE recommended methodology.[36,48]

The company applied the balancing weights to the IPD data of the index study to estimate adjusted outcomes. For the time-to-event outcomes, the adjusted KM curves were estimated by a weighted KM

analysis and plotted alongside the KM curves of the unadjusted population and the corresponding population in the comparator study to illustrate the direction and the magnitude of the shift due to the adjustment.[48]

The relative effect of zanubrutinib versus the control arm in ALPINE (ibrutinib) on the outcomes of interest was quantified along with 95% CIs in the CS after applying the balancing weights to the patients included in ELEVATE-RR.[6,30,36] The indirect relative effect of zanubrutinib and comparator arm was then obtained using formula (1), in the scale of the linear combination:

$$RE_{zanubrutinib\ vs.\ comparator} = RE_{\substack{zanubrutiniob\ vs.\ control \\ in\ the\ re-weighted\ index\ study}} - RE_{\substack{comparator\ vs.control \\ in\ the\ comparator\ study}} \quad (1)$$

EAG comment: The EAG do not have any concerns about the methodology used in the CS.

3.3.2.4.2 Indirect comparison for zanubrutinib versus acalabrutinib using ALPINE and ASCEND in R/R CLL

Outcomes and methodology for the MAIC analysis of zanubrutinib versus acalabrutinib using ALPINE and ASCEND were the same as described in Section 3.3.2.4.1. As IRC-assessed PFS was the primary endpoint in ASCEND and a key secondary endpoint in ALPINE, all PFS analyses in the CS were conducted using IRC-assessed PFS only.[6,30,35]

To estimate the relative treatment effect on the time-to-event efficacy outcomes between zanubrutinib and acalabrutinib in the CS, IPD from ALPINE were combined with the reconstructed IPD of ASCEND.[6,30,35] CS Section B.2.9.3.1 outlines the methods for calculating the relative treatment effect on the time-to-event efficacy outcomes between the zanubrutinib and acalabrutinib, as previously described in Section 3.3.2.4.1.[6] The CS reported HRs along with 95% CIs for both for the unweighted and weighted Cox proportional regression models to provide naïve and MAIC-adjusted estimates of the relative efficacy.[6]

EAG comment: The EAG do not have any concerns about the methodology used in the CS.

3.3.2.5 Results

3.3.2.5.1 Indirect comparison for zanubrutinib versus acalabrutinib using ALPINE and ELEVATE-RR in R/R CLL

The follow-up in ELEVATE-RR was reported as a median of 40.9 months and was considered by the company as the most comparable to ALPINE (median: 24.3 months).[6,30,36]

Since ELEVATE-RR randomised participants only with del17p or 11q deletion (as well as participants with TP53 mutation),[36] the ITT population in ALPINE was restricted to the subset of "high-risk" participants to ensure comparability across populations in the CS.[30] The MAIC approach in the CS then used IPD from ALPINE and adjusted the ALPINE trial population to match the average baseline characteristics of the acalabrutinib arm in ELEVATE-RR.[30,36] The unadjusted population characteristics of the acalabrutinib monotherapy arm in ELEVATE-RR compared to the population in ALPINE were presented in the CS (Table 49).[6,30,36]

The summary of the population characteristics after matching by weights generated from both Model 1 and Model 2 are presented in Tables 3.26 and 3.27.

Table 3.26: Population characteristics of ELEVATE-RR versus ALPINE before and after matching – Model 1

Population characteristics		Active treatment arms		Control treatment arms	
		Acalabrutinib (N = 268)	Zanubrutinib Model 1 (ESS = 79)	Ibrutinib (ELEVATE-RR) (N = 265)	Ibrutinib (ALPINE) (ESS = 63)
IGHV mutation	Mutated (versus unmutated), %	16.70%	[redacted]	10.60%	[redacted]
Cytogenetic mutation subgroups	Del17p, %	45.30%	[redacted]	45.30%	[redacted]
	Del11q, %	62.60%	[redacted]	66.10%	[redacted]
	TP53 mutation, %	37.40%	[redacted]	42.30%	[redacted]
Complex karyotype (≥ 3 abnormalities)	Yes (versus no), %	46.30%	[redacted]	47.20%	[redacted]
β2-microglobulin, mg/L	> 3.5 (versus ≤ 3.5), %	78.10%	[redacted]	80.80%	[redacted]
Number of prior therapies	≥ 4 (versus 1–3), %	12.40%	[redacted]	10.60%	[redacted]
Bulky disease, LDi in cm	≥ 5 (versus < 5), %	47.80%	[redacted]	51.30%	[redacted]
Age, years	≥ 75 (versus < 75), %	16.40%	[redacted]	16.20%	[redacted]
	Median	66.00	[redacted]	65.00	[redacted]
Sex	Male (versus female), %	69.00%	[redacted]	73.20%	[redacted]
ECOG PS	2 (versus 0-1), %	7.50%	[redacted]	8.30%	[redacted]
Cancer type	CLL (versus SLL), %	100%	[redacted]	100%	[redacted]
Binet stage (CLL patients only)	A (versus C), %	12.60%	[redacted]	11.60%	[redacted]
	B (versus C), %	45.30%	[redacted]	42.60%	[redacted]

Source: CS, Table 52[6]
Source of studies in CS: ALPINE[30], ELEVATE-RR[36]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CLL-IPI = Chronic lymphocytic leukaemia international prognostic index; CIRS = Cumulative Illness Rating Scale; del11q/del13q = Deletion of the long arm of chromosome 11/13; del17p = Deletion of the short arm of chromosome 17; ECOG = Eastern

Population characteristics	Active treatment arms		Control treatment arms	
	Acalabrutinib (N = 268)	Zanubrutinib Model 1 (ESS = 79)	Ibrutinib (ELEVATE-RR) (N = 265)	Ibrutinib (ALPINE) (ESS = 63)
Cooperative Oncology Group Performance Status Scale; ESS = Effective sample size; IGHV = Immunoglobulin heavy chain gene; PS = Performance status; R/R = Relapsed/refractory; SLL = Small lymphocytic lymphoma; TP53 = Tumor protein P53 gene.				

Table 3.27: Population characteristics of ELEVATE-RR versus ALPINE before and after matching – Model 2

Population characteristics		Active treatment arms		Control treatment arms	
		Acalabrutinib (N = 268)	Zanubrutinib Model 2 (ESS = 87)	Ibrutinib (ELEVATE-RR) (N = 265)	Ibrutinib (ALPINE[30]) (ESS = 79)
IGHV mutation	Mutated (versus unmutated), %	16.70%	[redacted]	10.60%	[redacted]
Cytogenetic mutation subgroups	Del17p, %	45.30%	[redacted]	45.30%	[redacted]
	Del11q, %	62.60%	[redacted]	66.10%	[redacted]
	TP53 mutation, %	37.40%	[redacted]	42.30%	[redacted]
Complex karyotype (≥3 abnormalities)	Yes (versus no), %	46.30%	[redacted]	47.20%	[redacted]
β2-microglobulin, mg/L	> 3.5 (versus ≤ 3.5), %	78.10%	[redacted]	80.80%	[redacted]
Number of prior therapies	≥ 4 (versus 1–3), %	12.40%	[redacted]	10.60%	[redacted]
Bulky disease, LDi in cm	≥ 5 (versus < 5), %	47.80%	[redacted]	51.30%	[redacted]
Age, years	≥ 75 (versus < 75), %	16.40%	[redacted]	16.20%	[redacted]
	Median	66.00	[redacted]	65.00	[redacted]
Sex	Male (versus female), %	69.00%	[redacted]	73.20%	[redacted]
ECOG PS	2 (versus 0-1), %	7.50%	[redacted]	8.30%	[redacted]
Cancer type	CLL (versus SLL), %	100%	[redacted]	100%	[redacted]
Binet stage (CLL patients only)	A (versus C), %	12.60%	[redacted]	11.60%	[redacted]

Population characteristics		Active treatment arms		Control treatment arms	
		Acalabrutinib (N = 268)	**Zanubrutinib Model 2 (ESS = 87)**	**Ibrutinib (ELEVATE-RR) (N = 265)**	**Ibrutinib (ALPINE[30]) (ESS = 79)**
	B (versus C), %	45.30%	[redacted]	42.60%	[redacted]

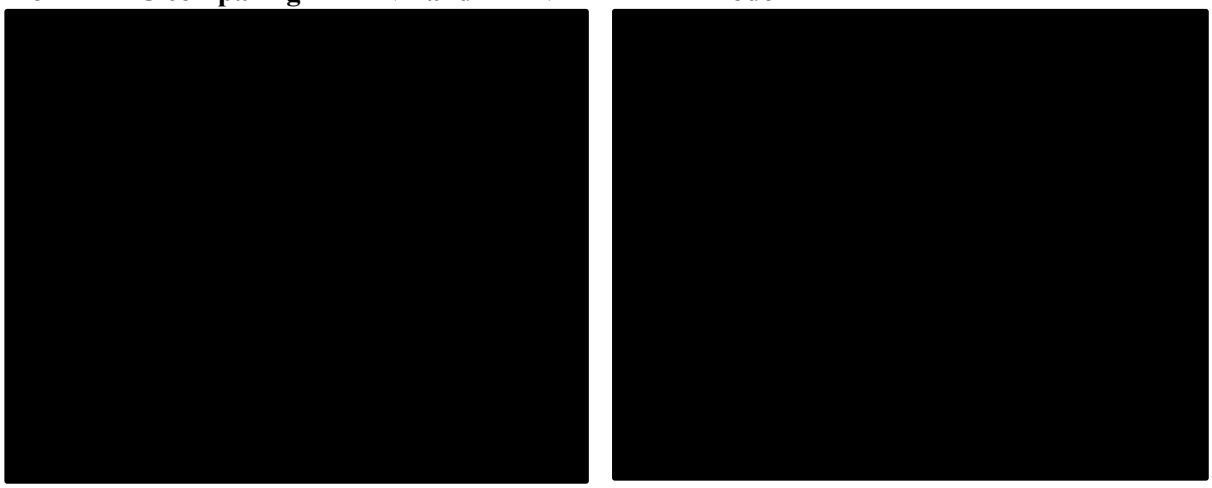
Source: CS, Table 53[6]
Source of studies in CS: ALPINE[30], ELEVATE-RR[36]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CLL-IPI = Chronic lymphocytic leukaemia international prognostic index; CIRS = Cumulative Illness Rating Scale; del11q/del13q = Deletion of the long arm of chromosome 11/13; del17p = Deletion of the short arm of chromosome 17; ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; ESS = Effective sample size; IGHV = Immunoglobulin heavy chain gene; PS = Performance status; R/R = Relapsed/refractory; SLL = Small lymphocytic lymphoma; TP53 = Tumor protein P53 gene.

After matching, all matched baseline characteristics were balanced (i.e. sufficiently similar) between the trials as demonstrated in the histograms of normalised weights, which are presented in Figures 3.8 and 3.9 for Model 1 and Model 2 respectively.[6]

Figure 3.8: Distribution of the normalised weights for zanubrutinib (left) and ibrutinib (right) from MAIC comparing ALPINE and ELEVATE-RR – Model 1

Source: CS, Figure 27[6]
Abbreviations: ESS = effective sample size; MAIC = matching-adjusted indirect comparison.

Figure 3.9: Distribution of the normalised weights for zanubrutinib (left) and ibrutinib (right) from MAIC comparing ALPINE and ELEVATE-RR – Model 2



Source: CS, Figure 28[6]
Abbreviations: ESS = effective sample size; MAIC = matching-adjusted indirect comparison.

The MAIC results for IRC- and INV-assessed PFS and OS both before and after matching are summarised in Table 3.28.[6] Both IRC-assessed PFS and INV-assessed PFS were available from ELEVATE-RR,[36] hence six MAICs were conducted.

Table 3.28: Summary of MAIC results for zanubrutinib versus acalabrutinib for patients with R/R CLL – ELEVATE-RR

	PFS (IRC)		PFS (INV)		OS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Pre-matching						
Model 1						
Model 2						

Source: CS, Table 54[6]
Abbreviations: CI = Confidence interval; CLL = Chronic lymphocytic leukaemia; HR = Hazard ratio; IRC = Independent review committee; INV = investigator-assessed; MAIC = Matching-adjusted indirect comparison; OS = Overall survival; PFS = Progression-free survival.

In Model 1, there was no statistically significant difference in either IRC-assessed PFS (HR , 95% CI) or INV-assessed PFS (HR , 95% CI) between zanubrutinib and acalabrutinib.[6] Similarly, there was no statistically significant difference in OS between zanubrutinib and acalabrutinib (HR , 95% CI).[6]

The company also stated that the results of Model 2 were consistent with Model 1, showing there was no statistically significant difference between zanubrutinib and acalabrutinib in IRC-assessed PFS (HR , 95% CI), INV-assessed PFS (HR , 95% CI), or OS (HR , 95% CI).[6] Across all outcomes and models, there was no statistically significant difference between zanubrutinib and acalabrutinib.[6]

The KM curves of IRC-assessed PFS for acalabrutinib and zanubrutinib (both pre- and post-adjustment) for Model 1 and Model 2 are presented in CS Figures 29 and 30.[6] Similarly, the KM curves of INV-assessed PFS for acalabrutinib and zanubrutinib (both pre- and post-adjustment) for Model 1 and Model 2 are presented in CS Figures 31 and 32.[6]

EAG comment: The EAG question the similarity of the duration of follow-up in ELEVATE-RR and ALPINE, as they clearly differ (median follow-up of 40.9 months in ELEVATE-RR and 24.3 months in ALPINE).[30,36] The EAG do not have any major concerns but the trial with the shorter duration of follow-up should be associated with less events and may not have the power to detect any differences between interventions that may or may not be present. The EAG agrees with the company that the matched baseline variables were generally well balanced.

The EAG note that the correct interpretation was applied to the results in this part of the CS (Section B.2.9.2.2) but this is later conflated with non-inferiority.[6,50] The company's claim of non-inferiority rather than no evidence of a difference is not correct based upon the data presented. This is because none of the MAICs reported in the CS demonstrate that zanubrutinib is non-inferior to acalabrutinib in either an untreated or R/R CLL population.[6,50] In all the MAICs, the 95% CIs clearly show there is a possibility that survival in participants using zanubrutinib could be worse than acalabrutinib.

The EAG acknowledges that the CS reported an appropriate assessment of the PH assumption for both IRC-assessed and INV-assessed PFS after population adjustment in both Model 1 and Model 2 in CS Section B.2.9.2.3 (p.129).[6] The EAG accepts the company view that there was no concerning evidence to doubt the PH assumption.

3.3.2.5.2 Indirect comparison for zanubrutinib versus acalabrutinib using ALPINE and ASCEND in R/R CLL

A summary of the population characteristics after matching by weights generated from both Model 1 and Model 2 are presented in Table 3.29.

Table 3.29: Population characteristics of the ASCEND versus ALPINE after matching

Population characteristics		**Acalabrutinib (N = 155)**	**Zanubrutinib Model 1 (ESS = 143)**	**Zanubrutinib Model 2 (ESS = 103)**
IGHV mutation	Unmutated (versus mutated), %	23.9%	[redacted]	[redacted]
Cytogenetic mutation subgroups	Del17p, %	18.1%	[redacted]	[redacted]
	Del11q, %	25.2%	[redacted]	[redacted]
	[12] TP53 mutation, %	25.2%	[redacted]	[redacted]
Number of prior therapies	2, %	25.8%	[redacted]	[redacted]
	3, %	11%	[redacted]	[redacted]
	≥ 4,%	10.3%	[redacted]	[redacted]
Bulky disease	LDi in cm, 5 (versus < 5)	49.0%	[redacted]	[redacted]
Age	75 (versus < 75)	21.9%	[redacted]	[redacted]
Sex	Male (versus female), %	69.7%	[redacted]	[redacted]

Population characteristics		Acalabrutinib (N = 155)	Zanubrutinib Model 1 (ESS = 143)	Zanubrutinib Model 2 (ESS = 103)
Geographic region	US and Canada (versus Europe)	5.2%	[redacted]	[redacted]
	Australia and New Zealand (versus Europe)	5.8%	[redacted]	[redacted]
	Asia (versus Europe)	4.5%	[redacted]	[redacted]
Rai stage III-IV	(versus 0-II), %	41.9%	[redacted]	[redacted]
ECOG PS	2 (versus 0-1), %	37.4%	[redacted]	[redacted]
Prior therapy	Purine analogue, %	70.3%	[redacted]	[redacted]
	Anti-CD20 antibody, %	83.9%	[redacted]	[redacted]
	Alkylators other than bendamustine, %	85.8%	[redacted]	[redacted]
	Bendamustine, %	30.3%	[redacted]	[redacted]

Source: CS, Table 58[6]
Source of studies in CS: ALPINE[30], ASCEND[35]
Abbreviations: ECOG PS = European Cooperative Oncology Group performance status; IGHV = immunoglobulin heavy chain gene; LDi = longest diameter.

After matching, all matched baseline characteristics appeared to be well balanced between the trials, as demonstrated in the histograms of normalised weights presented in Figures 3.10 and 3.11 for Model 1 and Model 2 respectively.

Figure 3.10: Distribution of the normalised weights for MAIC comparing ALPINE and ASCEND – Model 1

[redacted]

Source: CS, Figure 37[6]
Abbreviations: ESS = effective sample size; MAIC = matching-adjusted indirect comparison.

Figure 3.11: Distribution of the normalised weights for MAIC comparing ALPINE and ASCEND – Model 2

Source: CS, Figure 38[6]
Abbreviations: ESS = effective sample size; MAIC = matching-adjusted indirect comparison.

The MAIC results for IRC-assessed PFS and OS both before and after matching are summarised in Table 3.30.

Table 3.30: Summary of MAIC results for zanubrutinib versus acalabrutinib for R/R CLL

	PFS (IRC)		OS	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**
Pre-matching				
Model 1				
Model 2				

Source: CS, Table 59[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; OS = Overall survival; PFS = Progression free survival; R/R = Relapsed/refractory.

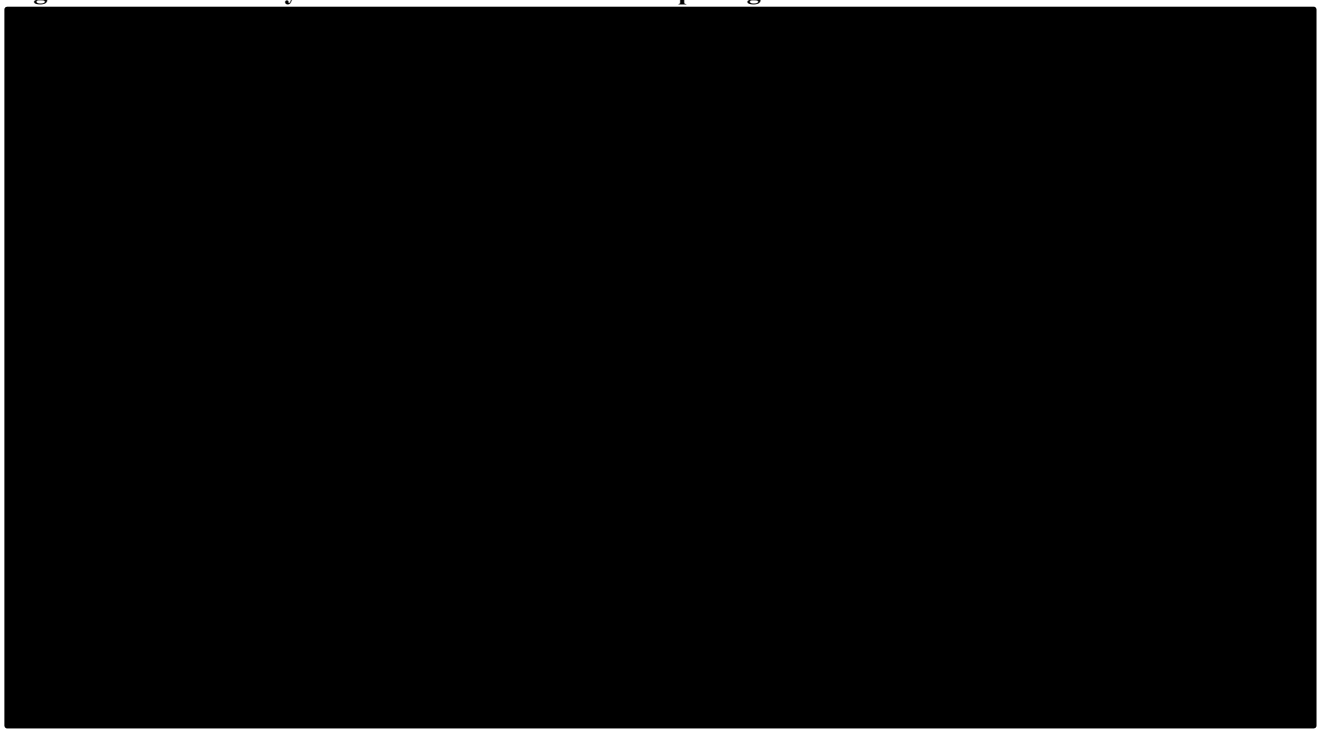
There was no statistically significant difference in IRC-assessed PFS between zanubrutinib and acalabrutinib in Model 1 (HR , 95% CI). Similarly, there was no statistically significant difference in OS between zanubrutinib and acalabrutinib (HR , 95% CI). The results of Model 2 were consistent with Model 1, demonstrating no statistically significant difference between zanubrutinib and acalabrutinib in IRC-assessed PFS (HR: ; 95% CI,) or OS (HR: ; 95% CI,).[6]

The KM curves of IRC-assessed PFS for acalabrutinib and zanubrutinib (both pre- and post-adjustment) are presented for Model 1 and Model 2 are presented in Figure 3.12 and Figure 3.13.

Figure 3.12: KM Analysis of PFS-IRC for MAIC comparing ALPINE and ASCEND – Model 1

Source: CS, Figure 39[6]
Abbreviations: IRC = Independent Review Committee; KM = Kaplan-Meier; MAIC = Matching-adjusted indirect comparison; PFS = progression free survival.

Figure 3.13: KM Analysis of PFS-IRC for MAIC comparing ALPINE and ASCEND – Model 2



Source: CS, Figure 40[6]
Abbreviations: IRC = Independent Review Committee; KM = Kaplan-Meier; MAIC = Matching-adjusted indirect comparison; PFS = Progression-free survival.

There is little change in the pre- and post-matching KMs for zanubrutinib, suggesting that the populations in ALPINE and ASCEND were relatively well-balanced.[30,35]

EAG comment: The EAG agree with the CS that the baseline characteristics between intervention arms were well balanced. The EAG note that the correct interpretation was applied to the results in this part of the CS but as described in Section 3.3.2.1.2, this is later conflated with non-inferiority.[6,50]

The EAG acknowledges that an appropriate assessment of the PH assumption for IRC-assessed PFS after population adjustment in both Model 1 and Model 2 in CS Section B.2.9.3.3 was reported.[6] The EAG accepts the company view that there was no concerning evidence to doubt the PH assumption.

3.4 Critique of the indirect comparison and MAIC approach

The EAG agree that conducting MAIC analyses was appropriate for informing the decision problem given the evidence identified in the CS. However, the EAG refer to the critique in Section 3.1.1 and question whether the searches could be more comprehensive and, if so, whether more evidence to inform the entire network could have been identified. The EAG acknowledge that heterogeneity was present and the rationale for conducting MAIC analyses as described in the CS appeared reasonable.

Although the company justified the exclusion of the RESONATE trial as outlined in Section 3.1.5, the EAG would have attempted to utilise all available evidence from trials that reported zanubrutinib as an intervention. While it may have not been considered necessary to inform the assessment of efficacy of zanubrutinib versus ibrutinib in patients with R/R CLL, it would have added to the wider network of evidence in an area which is sparse in the CS.

In a MAIC, the reliability of the analyses depends on the successful matching of the population. The distribution of weights assigned to participants in the index trial in a MAIC must be carefully assessed to ensure these do not give large influence to specific subgroups or individuals. The company conducted anchored analyses where possible and appeared to consider pertinent prognostic factors associated with this area. In this respect, the EAG acknowledge that the company have made a good attempt with the evidence identified in the CS, although most MAICs were unanchored due to the absence of common comparators.

A MAIC can only match for observed characteristics and, as such, heterogeneity in the MAICs presented in the CS may still be present, especially given that the random process is compromised in the conduct of a MAIC. While the EAG believe there was sound rationale for not selecting some prognostic factors as matching variables to maximise the ESS, their omission could be an additional source of heterogeneity and confounding. The EAG acknowledge that there were limited data available in any of the MAIC analyses. Therefore, the claim of non-inferiority rather than no evidence of any difference due to limited data and imprecision in effect estimates is a concern for the EAG.[50] None of the MAICs reported in the CS show zanubrutinib to be non-inferior to acalabrutinib in either an untreated or R/R CLL population.[6,50] The EAG consider the company's conclusions are based on inappropriately conflating a lack of statistical significance with non-inferiority or equivalence.[20,50] The EAG believe there is insufficient evidence of non-inferiority for zanubrutinib compared with other treatments included in the MAIC analyses in both untreated CLL and R/R CLL.[50]

3.5 Additional analyses conducted by the EAG

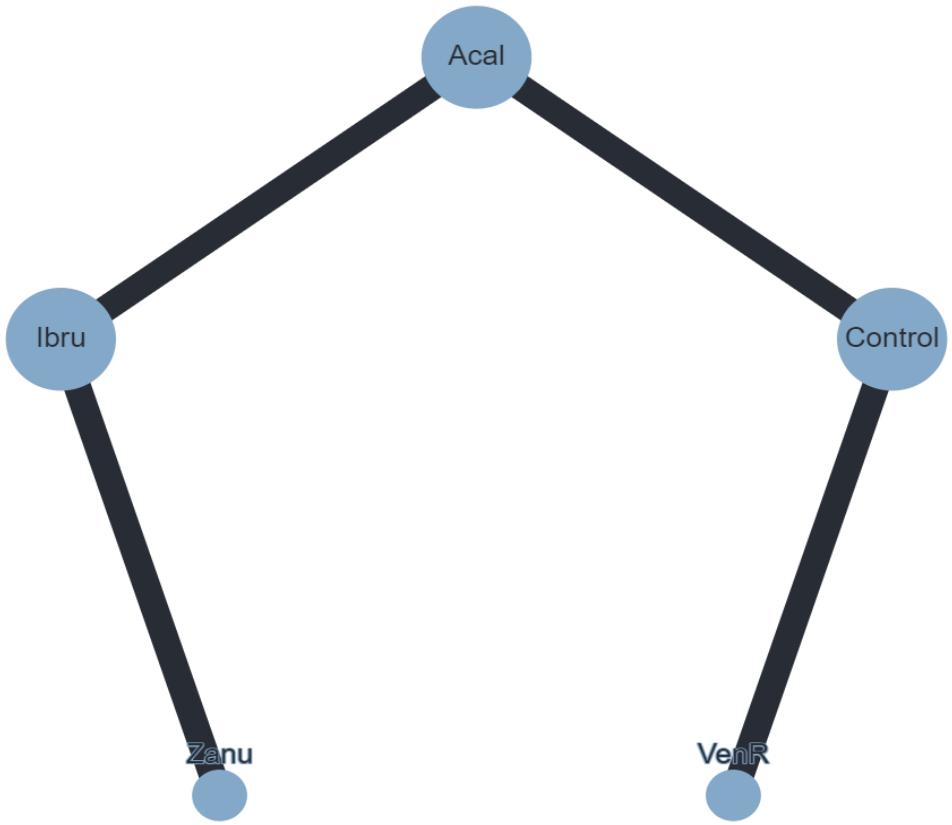
3.5.1 Scoping potential comparison of VenR versus zanubrutinib

As outlined in Section 2.2, the EAG disagreed with the company decision to exclude VenR as a relevant comparator in the R/R population. As VenR was excluded from the company's decision problem, the company did not include VenR in the SLR reported in the CS and did not conduct MAIC analyses of the effectiveness of zanubrutinib compared with VenR.

Since the EAG do not have access to IPD for any technologies in this topic area, we could not conduct MAIC analyses. However, the EAG examined whether it was possible to assemble a connected network of interventions that could potentially estimate the comparative effectiveness of zanubrutinib and VenR using network meta-analysis (NMA) of aggregate data (see Figure 3.14). In addition, this scoping exercise enabled an initial examination of whether it would have been possible for the company to conduct MAIC analyses between zanubrutinib and VenR. Given the limited time available for this appraisal, data for VenR (reported in TA561) was used to supplement data from studies identified in the company SLR.[3]

There are several limitations to this scoping exercise. First, it is beyond the time limits of the EAG critique to conduct a new literature search to identify a comprehensive set of included studies for VenR in this population. Second, the node "Control" is broader than the EAG would prefer, including BR (the comparator in the MURANO trial) and investigators' choice of BR or idelalisib plus rituximab (I-R) (the comparator in the ASCEND trial).[35,51] Although ASCEND found similar outcomes for either of the investigators' choice comparators, uncertainties remain regarding the comparability between comparators included in the MURANO and ASCEND trials. Third, ELEVATE-RR includes only "high-risk" patients with 17p deletion or 11q deletion,[36] whereas the other three trials (MURANO, ASCEND, ALPINE) included a combination of "high-risk" and "low-risk" patients.[30,35,51] Therefore, it is unclear whether the consistency (or transitivity) assumption between direct and indirect evidence would be valid. Fourth, Figure 3.14 shows that, although there is a network that connects zanubrutinib and VenR, the structure of the network means any comparison is likely to be highly uncertain.

Figure 3.14: Network diagram comparing zanubrutinib and VenR



Source: Created by the EAG
Abbreviations: Acal = Acalabrutinib, Ibru = Ibrutinib; VenR = Venetoclax-rituximab; Zanu = Zanubrutinib.

Similar challenges were encountered in TA561.[3] Similar to the EAG NMA in that appraisal, the NMA conducted by the EAG here used additional evidence outside of RCTs to strengthen the network. In this current analysis (see Figure 3.15), the EAG made the following changes:

- used the unanchored MAIC estimates (Models 1 and 2) for zanubrutinib versus acalabrutinib reported in the CS (from ASCEND and ALPINE); and
- removed the acalabrutinib versus ibrutinib comparison (from ELEVATE-RR) as these data were a potential threat to the consistency assumption of the NMA.

Figure 3.15: Amended network diagram comparing zanubrutinib and VenR (using additional MAIC estimates from CS)

Source: Created by the EAG
Abbreviations: Acal = Acalabrutinib, Ibru = Ibrutinib; VenR = Venetoclax-rituximab; Zanu = Zanubrutinib.

The EAG used the netmeta package in R to conduct an NMA for PFS and OS outcomes (see Table 3.31 3.31).[52] The NMA estimates were very uncertain, as demonstrated by very wide 95% CIs. These estimates suggest it is possible VenR is associated with greater PFS and OS compared with zanubrutinib. However, the 95% CIs are also consistent with the possibility that zanubrutinib is more effective than VenR. An unanchored MAIC may reduce the uncertainty of this comparison between zanubrutinib and VenR, and it is likely the company have the required data to conduct this analysis.

Table 3.31: NMA estimates comparing zanubrutinib with VenR in the R/R CLL population: PFS IRC-assessed and OS

Trial (source)	Comparison	PFS estimate reported in trial: HR (95% CI)	OS estimate reported in trial: HR (95
ALPINE[30]	Zanubrutinib versus ibrutinib	[redacted]	[redacted]
MURANO[3]	VenR versus BR	[redacted]	[redacted]

ASCEND[35]	Acalabrutinib versus BR or I-R	[redacted]	[redacted]
MAIC from CS[6]	Zanubrutinib versus acalabrutinib	[redacted]	[redacted]

Source: Created by the EAG based on CS, Table 59[6]
Abbreviations: BR = Bendamustine-rituximab; CI = Confidence interval; CLL = Chronic lymphocytic leukaemia; HR = Hazard r

3.5.2 Scoping potential comparison of VenO versus zanubrutinib

Based on the SLR reported in the CS (which did not include VenO), supplemented by a hand search of published STAs including the untreated CLL population, there may not be a connected network of RCTs. However, as in Section 3.5.1, including data from the MAIC analyses reported in CS (on this occasion zanubrutinib versus acalabrutinib in untreated CLL) led to a connected network (see Figure 3.16).

Figure 3.16: Network diagram comparing zanubrutinib and VenO

[redacted]

The EAG identified three studies in their scoping of the literature (MAIC analyses conducted in the CS, CLL14, and ELEVATE-TN). The EAG used the netmeta package in R to conduct an NMA for PFS and OS outcomes (see Table 3.32).[11,Rücker, 2023 #108,52] All four NMAs favoured zanubrutinib

compared with VenO. However, the 95% CIs were too wide to establish non-inferiority for both PFS and OS. It is possible that an unanchored MAIC could reduce uncertainty in this indirect comparison.

Table 3.32: NMA estimates comparing zanubrutinib with VenO in the untreated CLL population: PFS IRC-assessed and OS

Trial (source)	Comparison	PFS estimate reported in trial: HR (95% CI)	OS estimate reported in trial: HR (95% CI)	NMA Zanubrutinib compared with VenO: PFS HR (95% CI)	NMA Zanubrutinib compared with VenO: OS HR (95% CI)
MAIC in CS[6]	Zanubrutinib versus acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
CLL14[11]	VenO versus ChlorO	[redacted]	[redacted]		
ELEVATE-TN[34]	Acalabrutinib versus ChlorO	[redacted]	[redacted]		

Source: Created by the EAG based on data reported in Section B.2.9.1.2 of the CS (Table 59)[6] and TA663[10]
Abbreviations: CI = Confidence interval; ChlorO = Chlorambucil–obinutuzumab; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; HR = Hazard ratio; IRC = Independent review committee; NMA = Network meta-analysis; OS = Overall survival, PFS = Progression-free survival; R/R = Relapsed or refractory; VenO = Venetoclax-obinutuzumab.

3.6 Conclusions of the clinical effectiveness section

An SLR was undertaken to identify evidence addressing the NICE decision problem.[17] The critique of the reported search strategies and the rationale provided by the company for the selection of sources, time limits and search approaches bring the EAG to conclude that the searches were not of sufficient quality and robustness. Therefore, it would be expected that some potentially relevant studies would have been missed. Data were extracted from five RCTs but only two of these included a comparison with zanubrutinib that were directly relevant to the NICE decision problem; these are discussed below.

Untreated CLL population

SEQUOIA is a randomised, parallel assignment, open-label phase III study in participants with untreated CLL conducted across 14 countries including the UK.[29,37] The trial comprised four cohorts, of which two were considered relevant for the submission. Cohort 1 randomised participants to zanubrutinib or BR, while in Cohort 2 participants received zanubrutinib; the EAG believes the company's exclusion of the remaining two cohorts from the CS was acceptable. The EAG has concerns about the categorisation of the SEQUOIA population, as the company define all participants in Cohort 1 as "unfit" but, due to their ability to be eligible for BR in the trial, the EAG considers the participants to be "fit." The participants' eligibility for BR also means they are considered "fit" by the standards of the BSH guidelines.[2] The EAG appreciates that evidence in the "fit" population is sparse but has concerns about the data from SEQUOIA Cohort 1 being used as a proxy for the "unfit" population. Furthermore, the company did not establish non-inferiority for all outcomes, meaning that the assumptions necessary for a CMA approach to be valid have not been met.[41] Although zanubrutinib

was superior against BR for PFS and response rate, non-inferiority was not established for OS.[50] Finally, SEQUOIA did not measure TTTF, a key outcome in the NICE decision problem. As such, the EAG are unable to comment on the clinical effectiveness of zanubrutinib on TTTF for those with untreated CLL.

A NMA was deemed to be inappropriate by the company, so a MAIC was conducted using SEQUOIA and ELEVATE-TN,[29,34] which provided indirect evidence of zanubrutinib versus acalabrutinib, one of the comparators in the NICE scope. The MAIC analyses showed no statistically significant difference between zanubrutinib and acalabrutinib for survival outcomes in the untreated CLL population. The CS reported that zanubrutinib was, at the very least, non-inferior to acalabrutinib.[6] In contrast, the EAG concluded that it is highly uncertain whether zanubrutinib is non-inferior to comparator treatments in the untreated CLL population since the 95% CI in the MAIC analysis was too wide to conclude non-inferiority (see Section 4.3.6.2).[50]

R/R CLL population

ALPINE is an ongoing, randomised, parallel assignment, open-label phase III study in 652 participants with R/R CLL conducted across 14 countries, including the UK.[6,30,38] The participants had to be relapsed or refractory to at least one prior systemic therapy for CLL. The trial compared zanubrutinib with ibrutinib and assessed multiple outcomes, including INV-assessed ORR as the primary outcome and INV- and IRC-assessed PFS as the key secondary outcomes. Most trial participants were white and were randomised at sites in Europe, including the UK. Although the population in the ALPINE trial were generally healthier than what would be seen in NHS practice, the EAG were satisfied that the population were generalisable to in NHS clinical practice. The EAG requested clarifications regarding the comorbidities participants presented with at the start of the trial. The EAG are satisfied that the comorbidities the trial participants had at the start of the trial would not have affected the results.

MAICs were conducted in the R/R CLL population to form indirect comparisons of zanubrutinib with acalabrutinib and ibrutinib using the ALPINE, ELEVATE-RR and ASCEND trials to form the basis of the results.[30,35,36] The MAIC analyses were similar to the findings in the previously untreated population, finding no statistically significant difference between zanubrutinib and its comparator for survival outcomes in the R/R CLL population. As with the untreated CLL population, the EAG concluded there was insufficient evidence to demonstrate non-inferiority between zanubrutinib and the comparators considered in the MAIC analyses.[50] The 95% CIs in each MAIC analysis in the R/R CLL population were too wide to draw firm conclusions about relative effects (see Section 4.4.6.2).

4 COST-EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

This section is concerned with the review of cost-effectiveness evidence, which is provided by the company in CS Appendices D and G.[16,53] It also covers the search for additional parameters important to the economic model, such as the measurement and valuation of health effects, healthcare resources and costs (CS Appendices D, H and I).[16,54,55]

4.1.1 Searches performed for cost-effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost-effectiveness and for model inputs (i.e. health state utilities and resource use and costs) presented in the CS.[6]

4.1.1.1 Searches for cost-effectiveness analysis review

The company conducted the original searches on 01 July 2022, no further update searches have been reported. The company searched for cost-effectiveness, HRQoL, cost and resource use studies in a combined search of electronic bibliographic databases, including Embase, Embase Classic and MEDLINE via Embase.com. The company provided a single search strategy for both the clinical and economic studies search undertaken in Embase.com in CS Appendix D (Table 1).[16] The searches were limited to publication date between 01 January 2007 and 01 July 2022; the company provided justification for this time limit. An English language limit was used but no rationale reported. The company used an 'Economic filter' and a 'Quality of life' filter for the identification of cost-effectiveness, HRQoL, cost and resource use studies in CS, Appendix D (Table 1).[16]

Additional grey literature searches were performed to identify economic studies in three databases and the searches were reported separately: the School of Health And Related Research Health Utility Database (ScHARRHUD; CS, Appendix D, Table 3); EuroQol (CS, Appendix D, Table 4); and the Centre for Reviews and Dissemination (CRD) HTA and NHS Economic Evaluation Database (EED) databases (CS, Appendix D, Table 5).[16]

A summary of the CS search-related information is provided in Table 4.1.

Table 4.1: Summary of the searches undertaken for economic evaluations

Resource category	Resource	Host source	Date Range	Date search	Search strategy/terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	Embase	Embase interface	01.07.2007-01.07.2022	01.07.2022	Yes	Yes	Yes
	MEDLINE						
	Embase Classic						
	CENTRAL	Cochrane Library interface			Yes	Yes	Yes
	Cochrane Clinical Answers				No	No	NA
Grey literature	ScHARRHUD	NR	NR	01.07.2022	Yes	Yes	Yes
	EuroQol	NR	After 2007[b]				NR
	HTA and NHS EED	University of York website					Yes
	scottishmedicines.org.uk						

Source: Based on information presented in CS, Appendix D[16]

[a] The company provided a single SLR covering Embase, MEDLINE and Embase Classic. The EAG requested in the clarification letter individual search strategies including the following information: URL and platform of the database used, name of the database (with time coverage), date when the search was run, and number of retrieved records per database. As the Company failed to provide this information, the search strategy terms and the number of hits per line for each resource can not be verified by the EAG

[b] No precise dates given for the start of the search date range, the search string shows limitation applied for published after 2007, Table 4 and Table 5.[16]

Abbreviations: CENTRAL = Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; N = number; NA = not applicable; NR = not reported; NHS HTA and EED = National Health Service Health Technology Assessment and Economic Evaluation Database; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCHARRHUD = School of Health And Related Research Health Utility Database.

EAG comment: The EAG critically appraised the searches using the PRESS checklist and the latest NICE methods manual.[18,19] The EAG requested that the company submit individual search strategies for each of the databases searched via Embase.com, providing additional search information such as the name and date coverage of the databases at the time of searching, the date in which the search was run and the number of hits per line. The company responded reiterating that they only ran one general search via Embase.com, searching across multiple databases (Embase, MEDLINE and Embase Classic).[12] The inappropriateness of the use of Embase Classic has already been discussed in Section 3.1.1. Likewise, the EAG is unable to verify whether potentially relevant MEDLINE records may have been missed due to the automatic mapping performed by Embase.com (see Section 3.1.1). The number of records retrieved per search line was shown, as might be expected when using the PRISMA-S reporting guidance.[21] As also discussed in Section 3.1.1, the reported date of search being at least nine months ago raises issues with the currency of the evidence included in this submission. The EAG acknowledge that this may be a common concern of the HTA process and its variable timelines.

According to established guidelines for conducting technology assessments, "it is recommended that if the assessment is to serve as a basis for healthcare decision-making, this period should be as short as possible. Ideally less than 6 months before publication".[27]

As the company undertook one SLR and applied filters to identify potential studies with economic data, the EAG requested further information about the origin and performance of the filters used. The company's response informs of the provenance of such filters from SIGN.[12] Based on the search strategy appraisal undertaken the EAG has identified a disagreement between the source of the filters and the actual filters used. SIGN has only one economic study type filter (pragmatic and untested) available in their website,[56] which appears to have been modified by the company as it contains two additional search concepts that were not present in the original SIGN filter.[57] No justification for this alteration has been provided and, as discussed in Section 3.1.1, the EAG is unable to ascertain the impact of this modification on the performance of this filter. Additionally, a similar alteration on a published and validated filter for Health State Utility Values (HSUV) has been detected in CS Appendix D (Table 1).[16] The EAG requested that the company provide the original publication where this HSUV filter is tested and results of its performance.[12] The company responded with information for the sensitivity performance across three HSUV filters and bibliographic information for conference presentations of the search filters, which do not provide specific information of the HSUV filter reported by the company and therefore do not answer the questions raised by the EAG.[12] To the EAG's knowledge, there are three possible HSUV filters created in MEDLINE (Ovid) which have been validated and published in the International Journal of Technology Assessment in Health Care.[58] The filter reported in the search strategy appears to be an adaptation of one of those developed in MEDLINE (Ovid) to the Embase.com interface. Filter adaptation is not unusual, although in line with good practice standards the EAG would have preferred if the company transparently reported those adaptations and cited the original source. Alteration of a validated and published filter also changes the precision and performance; the company did not provide evidence of performing sensitivity testing of the adapted filter, therefore the EAG is unable to ascertain the performance of the adapted filter for the retrieval of HSUV studies.

The reported searches in ScHARRHUD and EuroQol databases were focused on population search terms only. The EAG appraisal of the strategies notes the lack of additional spelling e.g. "leukemia," acronyms such as "CLL" and other alternative search terms that could have been used to maximise the sensitivity of the search. The EAG notes that using the alternative spelling for "leukemia" would have retrieved at least one potentially relevant result in ScHARRHUD.

Table 5 in CS Appendix D presents the search strategy for the NHS EED and HTA databases via the CRD website.[16] Although the content of these databases has not been updated since 2015 and 2018 respectively, the company does not provide a rationale for not searching alternative platforms such as the International Network of Agencies for Health Technology Assessment (INAHTA) HTA database (https://database.inahta.org/), where the HTA database was transferred and is being kept up-to-date, or the CEA Registry (https://cear.tuftsmedicalcenter.org/) to identify potentially relevant grey literature reports and studies published after 2018.

Furthermore, the reported searches in CS Appendix D (Table 5) include inadequate search terms for the study types 'Economic filter' and 'QoL filter'.[16] As NHS EED solely contains records of economic evaluations, the strategy used to search this database need only contain terms related to the subject area.[39] The EAG noted that the PRISMA flowchart incorrectly reports the results of the searches in these two databases (CS Appendix D, Figure 1).[16]

Overall, after assessment of the range of sources searched, the methods used to search and the limits imposed to the searches, the EAG questions the comprehensiveness and validity of these searches for the identification of relevant and up-to-date evidence on the NICE decision problem.[17]

4.1.1.2 Searches for model inputs

The search for model inputs focused on health state utilities and cost and resource use studies; this search was integrated into the search for cost-effectiveness described in Section 4.1.1.1. As noted in Section 4.1.1.1, a study design filter was used for health state utilities, which the company provided a URL for.[16] As already noted, no supporting information on the rationale for the selection and use of this filter, as well as its origin and filter performance (sensitivity, specificity and recall), was provided. Additional grey literature searches were performed to identify HRQoL studies in a number of databases and reported separately: ScHARRHUD (CS, Appendix D, Table 3); EuroQol (CS, Appendix D, Table 4); and the CRD HTA and NHS EED databases (CS, Appendix D, Table 5).[16] No separate filters were reported for cost and resource use studies and no separate terms were included to identify resource use studies.

EAG comment: The company reported the use of a QoL study design filter and a corresponding URL. The EAG note that the referenced URL did not link to the pre-tested peer reviewed filter study. Additionally, the study filter used includes alterations to the subject headings without justification. Any manipulation in the translation of filters should be reported, as this will impact sensitivity and specificity of the filter performance. It is unclear if all relevant resource use and cost analyses were identified. The extent to which this is material is unclear to the EAG.

4.1.2 Eligibility criteria for inclusion of economic evaluations, health state utilities studies and cost and resource use studies

4.1.2.1 Eligibility criteria for inclusion of economic evaluations

CS Appendix D (Table 8; reproduced as Table 4.2) provides the eligibility criteria used to screen economic evaluation retrieved from the searches.[16] The criteria provided are based on patients, intervention, comparator, outcomes, and study type (PICOS). The company also included criteria surrounding publications type.

All abstracts were screened against the review questions and the eligibility criteria by two independent reviewers, followed by arbitration of disagreements by a third, independent reviewer.[16] The full texts of relevant studies were examined in more detail against the selection criteria to determine a final list of included studies. Again, this was conducted by two independent reviewers, with arbitration by a third

independent reviewer in case of any disagreement. Reasons for exclusion were detailed for studies excluded at the full text review stage. A PRISMA flow diagram was populated on the basis of this process.[16]

Table 4.2: Eligibility criteria for inclusion of economic evaluations

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with chronic lymphocytic leukaemia	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	Brukinsa® (zanubrutinib) Imbruvica® (ibrutinib) Calquence® (acalabrutinib) Levact® (bendamustine) Vencylxto® (venetoclax) Mabthera®(rituximab) Fludara® (fludarabine) Cytoxan® (cyclophosphamide) Zydelig® (idelalsib) Gazyvaro® (obinutuzumab) Leukeran® (chlorambucil)	No intervention / comparators of interest
Outcomes	Cost per QALY gained Cost per life-year gained	No reported outcomes of interest, i.e., budget impact model outcomes
Study type	Economic evaluations:	Cost-benefit study Burden of disease study Resource use study Budget impact study
Publication type	Article, conference abstract, conference paper, article in press	Short survey Reviews Letters Comment articles
Language	English	Non-English

Source: CS, Appendix D, Table 8[16]
Abbreviations: QALYs = Quality-adjusted life years; SLR = Systematic literature review.

EAG comment: The eligibility criteria presented by the company are acceptable and cover all PICOS parameters. The company exclude cost-benefit studies but these are rarely performed in health care and, where studies do claim to be cost-benefit studies, they are more often cost analyses only.

4.1.2.2 Eligibility criteria for inclusion of health state utilities studies and cost and resource use studies

Tables 4.3 and 4.4, both taken from CS Appendix D (Table 9 and 10, respectively),[16] provide the criteria used to screen health state utilities studies and cost and resource use studies retrieved from the searches. For HRQoL publications, only studies which included Bruton tyrosine kinase inhibitor (BTKi) treatments (zanubrutinib, ibrutinib and acalabrutinib) were included. Similarly, resource use and costs studies had to include BTKi treatments. Furthermore, they had to adopt a UK cost perspective. The same process as outlined in Section 4.1.2.1 was followed to select studies for inclusion.

Table 4.3: Eligibility criteria for inclusion of health state utilities studies

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with chronic lymphocytic leukaemia	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	Any intervention	No intervention / comparators of interest
Outcomes	Utility scores Disutilities	No reported outcomes of interest
Study type	RCTs Non-RCTs Observational studies HRQoL elicitation studies HRQoL validation studies Economic evaluations: Cost-utility analysis EEACT	Individual case study reports
Publication type	Article, conference abstract, conference paper, article in press	Short survey Reviews Letters Comment articles
Language	English	Non-English

Source: CS, Appendix D, Table 9[16]
Abbreviations: EEACT = Economic evaluation alongside clinical trials; HRQoL = Health-related quality of life; RCT = Randomised controlled trial; SLR = Systematic literature review.

Table 4.4: Eligibility criteria for inclusion of resource use and cost studies

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with chronic lymphocytic leukaemia	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately

		for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	Any intervention	No intervention / comparators of interest
Outcomes	Unit costs Resource use Budget impact Cost of illness	No reported outcomes of interest
Study type	Cost study Burden of disease study Resource use study Economic evaluations: Cost-effectiveness analysis Cost-utility analysis Cost-benefit analysis Cost-minimisation analysis WTP studies EEACT	Individual case study reports
Publication type	Article, conference abstract, conference paper, article in press	Short survey Reviews Letters Comment articles
Language	English	Non-English
Source: CS Appendix D, Table 10[16] Abbreviations: EEACT = Economic evaluation alongside clinical trials; SLR = Systematic literature review; WTP = Willingness to pay.		

EAG comment: The EAG agrees that the eligibility criteria are generally suitable to fulfil the company's objective to identify utility, healthcare resource use and costs. However, the EAG is unclear why willingness to pay studies are included in the list of relevant studies for resource use and cost but not for health state utilities. Willingness to pay studies do not tend to report costs nor resource use and, if they did, it would be expected that they would be labelled as cost-benefit studies or cost-consequence analyses. However, it is plausible that they provide health state valuations, albeit using money as the numeraire or concurrently capture health state utilities using other methods.

The EAG also considers that VenR and VenO should have been included as comparators, as noted in Section 2.2. As such, data on costs, resource use and HRQoL should not have been restricted to BTKi treatments.

4.1.3 Conclusions of the cost-effectiveness review

The CS provided an overview of the different search strategies used to identify eligible studies that could be used to inform the development of and populate the cost-effectiveness model. The company conducted one integrated review for economic evaluations, health state utilities and resource use and cost studies.

EAG comment: The EAG notes limitations with the searches conducted and the difference in scope for the reviews of health state utilities and resource use and cost studies but considers this a reasonable restriction. Overall, the EAG considers that the review is sufficiently well conducted. The exception to this is the identification of HRQoL and health state utilities data. The EAG is of the view that the searches conducted may fail to identify all relevant information to the decision problem (see Section 3.1).

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	As listed in the scope developed by NICE[17]	Complied with the reference case.
Comparators	Acalabrutinib and ibrutinib	The EAG has concerns that VenO was not included as a comparator in the untreated CLL model and VenR was not included as a comparator in the R/R CLL model (see Section 2.3).
Perspective on outcomes	The outcome measures to be included considers include: • Overall survival • Progression-free survival • Time-to-treatment failure • Adverse effects of treatment • Heath-related quality of life	Overall, the company complied with the reference case. However, TTTF was not included as an outcome in the SEQUOIA trial.
Perspective on costs	NHS and PSS	Complied with the reference case
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company conducted a CMA. This approach assumes that zanubrutinib has the same benefits/effectiveness as both acalabrutinib and ibrutinib. A CUA was undertaken as a scenario analysis only. The EAG disagrees with the company's assumption of non-inferiority (see Section 3.4 and Section 3.5), and thus disagrees with the use of a CMA instead of a CUA as the company base-case analysis. The adoption of a CUA as the company's base-case may not have changed the conclusions but the EAG cannot be certain of

Element of health technology assessment	Reference case	EAG comment on company's submission
		this due to limitations with the modelling associated with the CMA assumption. Two separate economic models were developed; one for each populations. These were a semi-Markov model for the previously untreated population and a partitioned survival model for the R/R population.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	A lifetime 30-year time horizon was adopted for both economic models, which the EAG considers would be sufficient to capture the relevant outcomes had a CUA approach been adopted.
Synthesis of evidence on health effects	Based on systematic review.	An SLR was presented by the company, for which the EAG raised multiple concerns (see Section 3.1.1 and Section 3.1.3). The company applied a quality of life and Economic filter to these search results. In addition, the company searched NHS EED and HTA databases..
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D data was collected from the SEQUOIA trial for the untreated CLL population. No EQ-5D data was collected for the trial arm with del17p, so HRQoL data from patients without del17p were assumed to be applicable to the whole of the untreated population. EQ-5D data from the ALPINE trial was used for the R/R CLL population.
Source of data for measurement of health-related quality of life	Reported directly by patients and/ or carers.	HSUVs were sourced from previously accepted NICE TA689 and NICE TA561, after HSUVs generated for PF and PD from ALPINE and SEQUOIA were considered to lack face validity for lying above general UK population HSUVs. The EAG expressed concerns for the transparency of reporting in the source informing PD HSUVs. The EAG also notes that EQ-5D data was not collected

Element of health technology assessment	Reference case	EAG comment on company's submission
		for the "high-risk" untreated CLL Cohort 2 of SEQUOIA.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Complied with the reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No additional equity considerations were deemed necessary in this appraisal. Overall, the company complied with the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Complied with the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Complied with the reference case.

Source: Created by the EAG
Abbreviations: BR = Bendamustine-rituximab; CLL = Chronic lymphocytic leukaemia; CMA = Cost-minimisation analysis; CUA = Cost-utility analysis; del17p = 17p deletion; EAG = Evidence Assessment Group; FCR = Fludarabine, cyclophosphamide and rituximab; HRQoL = Health-related quality of life; HSUV = Health state utility value; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PSS = Personal social services; QALY = Quality-adjusted life year; R/R = Relapsed or refractory; UK = United Kingdom; VenO = Venetoclax-obinutuzumab; VenR = Venetoclax-rituximab combination.

The company developed two economic models for the two populations (untreated and R/R CLL). Section 4.3 discusses the development and population of the economic model for the previously untreated CLL population, while Section 4.4 discusses the development and population of the economic model for the R/R CLL population.

4.3 Summary of cost-effectiveness analysis for the untreated CLL population

The SLR conducted by the company did not identify any previous economic evaluations assessing zanubrutinib in patients with previously untreated CLL.[6]Therefore, a de novo model was developed, informed by previous NICE Technology Appraisals in CLL, which were used to justify key features including the modelling approach, time horizon, cycle length and the source of cost and utility value parameters (CS, Table 67).[6]

A CMA was selected by the company as the most suitable approach to evaluate zanubrutinib compared with acalabrutinib and ibrutinib in the untreated CLL population. Hence, this analysis aimed to estimate differences in costs across zanubrutinib, acalabrutinib, and ibrutinib assuming clinically equivalent outcomes for the untreated CLL population. This choice was justified by the company based on the results obtained by the MAIC comparing zanubrutinib with acalabrutinib in untreated patients performed by the company,[6] as well as results from the ALPINE trial comparing zanubrutinib with ibrutinib in R/R as a proxy for the untreated population considered "high-risk."[4]

4.3.1 EAG comment on company's review of cost-effectiveness evidence

See Section 4.1 for the EAG critique on the SLR performed by the company for both the untreated CLL and the R/R CLL populations.

4.3.2 Model structure

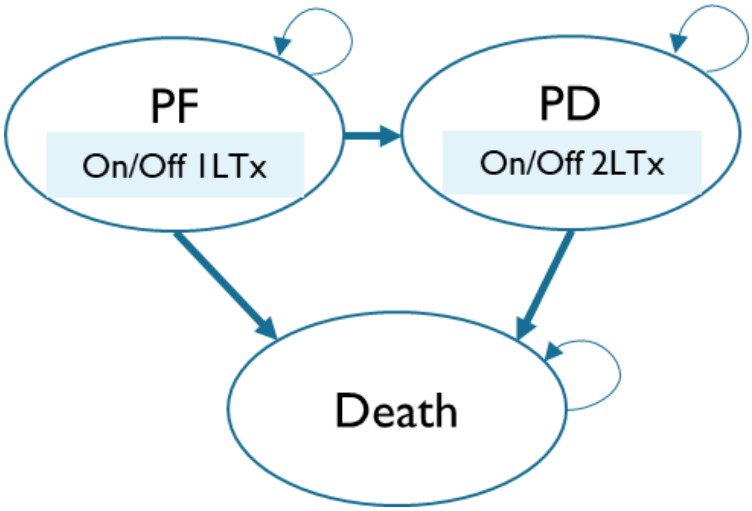
The company submitted two model-based economic analysis of zanubrutinib for the untreated CLL and the R/R CLL patient populations respectively. Both models were programmed in Microsoft Excel®.

The model for the untreated CLL population contained two subgroup analyses: zanubrutinib compared with acalabrutinib for "unfit" patients (i.e. those unsuitable for FCR or BR) without del17p; and zanubrutinib compared with both acalabrutinib and ibrutinib respectively for "high risk" patients (i.e. with del17p or TP53 mutation) unsuitable to receive CIT.

4.3.2.1 Health states/events and transitions

A three-health state semi-Markov structure was developed to model patients in the untreated CLL population. The three mutually exclusive health states were progression free (PF) or pre-progression, progressed disease (PD), and death (see Figure 4.1). All patients started in the PF health state and could either stay in PF, move to the PD state upon disease progression, or move to the death state. Once patients moved to PD, they either stayed in PD or died. During the PD state, PFS data from second-line treatments was used to model the costs of subsequent treatments. However, this did not affect the transitions between health states.

Figure 4.1 Health state structure used in the economic model of untreated CLL



Source: CS, Figure 44[6]
Abbreviations: PF = Progression-free; PD = Progressed disease; 1LTx = First-line treatment; 2LTx = Second-line treatment.

Transitions used in the model:

- PF to PD: Transitions from PF to PD were informed by time to progression data (with death events censored) from combining arms A and C of the SEQUOIA trial.[59]
- PF to Death: Pre-progression survival (PrePS) was informed by survival data from the combination of arms A, B and C of the SEQUOIA trial,[59] with the risk of death constrained on

the lower end by age- and sex-adjusted risk of death from the UK general population (to ensure patient risk of death was not lower relative to the general population).

- PD to Death: Due to data from SEQUIOA being considered too immature for this disease stage,[59] mortality after progression was informed by the post-progression survival (PPS) curves from the MURANO trial,[51] with risk of death constrained on the lower end by age- and sex-adjusted risk of death from the UK general population.

Treatment discontinuation: In the company base-case model, all patients starting at PF received first-line treatment until progression or death. After disease progression, patients were moved to second-line treatment, which was given until either end of treatment was reached, patients moved to the death state, or treatment discontinuation occurred while remaining in the PD state. PFS from the MURANO study was used as a proxy to estimate time on treatment for second-line therapies, in combination with treatment specific stopping rules.[51]

EAG comment: The EAG found the semi-Markov approach to be a flexible structure to model the disease that maximised the use of the evidence available if a CMA were considered to be an appropriate economic evaluation framework. The health states and transitions used were also considered appropriate for the context of the disease. However, following the critiques of the MAIC methodology and interpretation of the results presented in Sections 3.4 and 3.5, the EAG considers that uncertainty in the relative efficacy of zanubrutinib does not provide concrete evidence of non-inferiority, therefore undermining the core assumptions of the CMA.

The EAG is aware that a CUA approach was proposed by the company as a scenario analysis by using the PFS HRs from the MAIC as a replacement for time to disease progression (TTP) HRs for acalabrutinib. These results should be interpreted with caution as PFS may not map perfectly into TTP, which may lead to inaccuracies in the results. Furthermore, the exclusion of PrePS HRs from this scenario may introduce further inaccuracies.

4.3.3 Population

The company's economic analysis was structured to reflect two populations: previously untreated CLL patients and patients with R/R CLL. In the untreated analysis, model 1 compares two sub-populations:

1) zanubrutinib versus acalabrutinib for previously untreated adults "unfit" FCR or BR therapy based on arm A (Cohort 1) of the SEQUOIA trial;[59] and
2) zanubrutinib versus acalabrutinib or ibrutinib, for previously untreated adults with del17p and/or TP53 mutation, and in whom CIT is unsuitable, also referred to as "high-risk," and based on arm C (Cohort 2) of the SEQUOIA trial.[59]

Baseline characteristics were derived from the pooled arm A ("unfit" patients in Cohort 1 receiving zanubrutinib) and arm C ("high-risk" patients in Cohort 2 receiving zanubrutinib) of the SEQUOIA trial.[59] Patients were assumed to have a mean age of [redacted] years and [redacted] of patients were assumed to be female.[6] A body surface area (BSA) of 1.92 m^2 calculated from data pooled from data from arms A and C data of SEQUOIA was used to calculate the cost of second-line treatments.

The company base-case analysis presented the cost-effectiveness results for untreated CLL, which combined those who were "unfit" and "high-risk". The company also presented cost-effectiveness results for "unfit" untreated CLL and "high-risk" untreated CLL in the scenario analysis.

EAG comment: The EAG considers the paucity of evidence, particularly for the "unfit" untreated CLL patients without del17p and/or TP53 mutation, to be a major source of uncertainty. This is partially

addressed in the approach presented by the company, which utilises data on patients that would be considered as "fit" as a proxy for "unfit" untreated CLL patients (see Section 3.2.1.1). However, the EAG are uncertain whether the effectiveness results for zanubrutinib are different in an "unfit" population compared to a "fit" population and what such differences would have on the cost-effectiveness results.

The EAG has further concerns with the appropriateness of a MAIC that pools patient populations with and without del17p and/or TP53 (see Section 3.4), and the generalisability of the pooled results to both the "high-risk" with del17p sub-population, and the "unfit" without del17p untreated CLL sub-population when acalabrutinib is the comparator. The EAG also notes that evidence of the relative efficacy of zanubrutinib versus ibrutinib in the untreated "high-risk" CLL population comes from a trial using data on R/R CLL patients only.[30] The company also undertook a scenario analysis using data from their naïve comparison however the EAG consider these data to be subject to uncertainty due to the nature of this study being retrospective, and because potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison. This is critiqued in more detail in section 4.3.6.2.

4.3.4 Interventions and comparators

The intervention for the untreated CLL model was zanubrutinib administered orally twice daily as 160 mg per administration (composed of two 80 mg capsules). The company base-case did not assume a formal stopping rule; patients were instead assumed to continue treatment until either disease progression or death.[60] An alternative treatment discontinuation assumption was explored in the scenario analysis (see Section 5.1.1).

Acalabrutinib was used as a comparator for both the untreated CLL "unfit" and "high-risk" sub-populations and, in current practice, is administered orally twice daily as 100 mg per administration until either disease progression or death for both sub-populations.[61]

Ibrutinib was used as a comparator for the untreated CLL "high-risk" subgroup and, in current practice, is administered orally once daily as 420 mg per administration until either disease progression or death.[62]

The cost of subsequent treatments after disease progression were included in the untreated CLL model. All patients received VenR therapy after disease progression across all treatment arms. In current practice, venetoclax is administered for two years (26 model cycles) or until discontinuation or death. Rituximab is administered for six 28-day cycles until discontinuation or death.[63] Time to treatment discontinuation for second-line therapy was informed by the MURANO study.[51]

EAG comment: Treatment regimens are correctly represented in the base-case model in accordance with the CS and are consistent with the summary of product characteristics (SmPC) across all comparator arms of the untreated CLL population.

4.3.5 Perspective, time horizon and discounting

Both economic models presented by the company used four-week (28 day) cycles for a 30-year lifetime horizon and the analyses were undertaken from an NHS and PSS perspective. Both costs and utility values were discounted at a 3.5% rate in line with NICE guidelines.[19]

EAG comment: The EAG considers the time horizon as appropriate to capture the costs and benefits relevant to this intervention. The cycle length used in the model is deemed appropriate to capture disease progression and is in line with previous NICE Technology Appraisals (e.g. NICE TA689).[64]

4.3.6 Treatment effectiveness and extrapolation

The model used different data sources to inform pre-progression and post-progression survival for the untreated CLL population. TTP and PrePS curves were generated using data from SEQUOIA,[59] pooling arm A ("unfit" patients without del17p) with arm C ("unfit," "high-risk" patients with del17pand/or TP53 mutation) to align with the MAIC methodology (see Section 3.4). The base-case model used pooled SEQUOIA data to model both "unfit" and "high-risk" sub-populations. However, scenario analyses were presented using data from arm A and arm C independently to model the "unfit" and "high-risk" populations respectively.

As SEQUIOIA reports both IRC- and INV- assessments of trial data outcomes, the company selected IRC-assessed outcomes to extrapolate TTP and PrePS over the long-term due to IRC-assessed outcomes being the primary outcome of SEQUOIA.[6]

Under the CMA approach, the clinical effectiveness was assumed to be the same across all treatment arms. Parametric survival analysis was conducted by fitting six survival functions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) to IPD. Parametric models were fitted independently without the inclusion of a treatment-specific parameter. The CMA approach was argued to be justified by the company from the results of relative efficacy between zanubrutinib compared with acalabrutinib across two MAICs (see Section 3.3.2) and zanubrutinib compared with ibrutinib using head-to-head trial data from ALPINE.[30] Details of the approach presented in the CS of the methods used to select a parametric extrapolation and the evidence used to justify a CMA, along with their respective EAG critique are presented in Section 4.3.6.1 and Section 4.3.6.2.

4.3.6.1 Survival analysis and extrapolation methods

4.3.6.1.1 Time to progression (TTP)

TTP was derived directly using IPD from SEQUOIA at the 07 May 2021 data cut-off, combining arm A (N=241, reporting [redacted] ([redacted]) events at data cut-off) and arm C (N=111, reporting [redacted] ([redacted]) events at data cut-off). Statistical fit was assessed based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) coefficients. Results are presented in Table 4.6. The exponential and log-normal distributions had the best fit to the IPD data. The selection process also involved assessing PFS predictions in the pre-progression health state by combining both TTP and PrePS curves together. Moreover, the company decided to align the distribution functions for TTP and PrePS to provide a better representation of PFS.

Table 4.6: Goodness-of-fit statistics for IRC-assessed TTP – zanubrutinib (pooled SEQUOIA arm A and arm C)

Distribution	Zanubrutinib (stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Source: CS, Table 70[6]		

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; IRC = Independent review committee; TTP = time to progression.

Figure 4.2: IRC-assessed TTP with extrapolated parametric survival curves (pooled arm A and arm C from SEQUOIA)

Source: Recreated by the EAG based on CS Figure 46[6]
Abbreviations: IRC = Independent review committee; CLL = Chronic lymphocytic leukaemia; Gen. Gamma = Generalised gamma; KM = Kaplan-Meier; TTP = Time to progression; Zanu = Zanubrutinib.

EAG comment: [redacted] The company provided a visual assessment of TTP data for arm A and arm C independently in appendix M; however, this analysis did not compare the two arms together.[65]

The EAG considers that a statistical assessment of the progression hazards between the "unfit" (arm A) and "high-risk" (arm C) populations should have been provided using KM TTP data from both arms of SEQUOIA,[29] to better justify pooling the data together for use in the model. Furthermore, a statistical assessment of SEQUOIA outcomes across arm A and arm C was feasible and is likely to be informative from a clinical perspective.

In the absence of a statistical analysis between arm A and arm C, it is uncertain to the EAG whether data from the SEQUOIA trial suggested significant differences in disease progression across untreated CLL patients with del17p (arm A) versus patients without del17p (arm C). A scenario analysis was presented using parametric survival curves from data on arm A and arm C independently.

The AIC estimates reported in Table 4.6 present small differences across the parametric distributions, which makes the selection of a model primarily dependent on external evidence.

4.3.6.1.2 Pre-progression survival (PrePS)

To construct the PrePS curve, the company combined data from SEQUOIA arm A ("unfit" patients without del17p receiving zanubrutinib), arm B ("unfit" patients without del17p receiving BR therapy), and arm C ("high-risk" patients with del17p receiving zanubrutinib). The rationale behind pooling the data was the low number of death events observed in SEQUOIA by the 7 of May 2021 cut-off point: [redacted] events ([redacted]) in arm A; [redacted] events ([redacted]) in arm B; and [redacted] events ([redacted]) in arm C.

The methodology used by the company to generate the PrePS curve was to extrapolate IPD survival data from arms A and C, then extrapolate data from arm B independently. PrePS was then built as the average of both parametric extrapolations, assuming the same distribution for arms A and C data as for arm B data (see Figure 4.3). AIC and BIC coefficients for each survival curve are reported in Table 4.7. The exponential distribution showed the best fit to the data from both pooled arm A and arm C survival, and arm C survival from SEQUOIA.[59] The risk of mortality in the PrePS curve was constrained by the age- and sex-adjusted mortality risk from the UK general population as the minimum level of risk at the PF health state.

Table 4.7: Goodness-of-fit statistics for IRC-assessed PrePS (pooled SEQUOIA arm A and arm C for zanubrutinib compared to arm B for BR)

Distribution	Zanubrutinib (pooled arm A and arm C)		BR (arm B)	
	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 71, CS[6]
Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; BR = Bendamustine-rituximab; IRC = Independent review committee; PrePS = Pre-progression survival.

Figure 4.3: IRC-assessed PrePS with long-term extrapolations constrained by general population mortality used in the CS model

[redacted]

Source: Created by the EAG.
Abbreviations: CLL = Chronic lymphocytic leukaemia; CS = Company submission; Gen. Gamma = Generalised gamma; IRC = Independent review committee; KM = Kaplan-Meier; PrePS = Pre-progression survival
**Exponential and Generalised Gamma functions were almost equivalent.

Choice of distribution at the Pre-Progression state: To select the distribution used to model TTP and PrePS, the company compared PFS as a combination of both TTP and PrePS curves (assuming the same distribution in both) with expert opinion, which suggested that RESONATE-2 PFS was a suitable source of evidence.[31] A generalised gamma model applied to both TTP and PrePS was the distribution selected based on its PFS predictions at year eight ([redacted]) being closer to the RESONATE-2 trial (~60%).[31]

Treatment duration: The base-case model assumed BTKi-based first-line treatment was given until disease progression or death. An alternative assumption was presented for zanubrutinib in the scenario analysis, where treatment discontinuation was based on SEQUOIA data for zanubrutinib only,[59] as no data were found for acalabrutinib nor ibrutinib for treatment discontinuation.

EAG comment: Combining patient data on survival across multiple arms is a commonly used approach when a contextually short follow-up leads to a small number of events and the Kaplan-Meier curves are shown to be similar across said arms.

The statistical fit was similar across parametric distributions for each Kaplan-Meier curve (arm A and arm C versus arm B). However, the EAG does not consider the methodology used by the company to combine data across arms as a simple average between the two parametric extrapolations of arms A and C, and arm B separately, to be the most appropriate approach. It deviates from the standard approach of combining all data on an individual level and extrapolating from the pooled IPD. Nevertheless, the EAG does not expect this to have a significant impact on model results as the competing risk of death from the general population overtakes the risk from most parametric functions early in the model (except for the Gompertz extrapolation but this model was considered too pessimistic by the clinical expert consulted by the EAG). It is unclear to the EAG why the company did not pool the IPD across all arms before deriving the parametric PrePS curve.

From the information provided on the advisory board meeting organised by the company, it is unclear to the EAG whether experts were presented with TTP or PFS survival curves extrapolated from SEQUOIA.[44] Furthermore, the EAG considers the comparison made with the RESONATE-2 trial to be highly optimistic and potentially inappropriate, as this trial excluded patients with del17p,[31] while data from SEQUOIA, when combining arm A and arm C, contains almost one third of patients with this characteristic.

4.3.6.1.3 Post-Progression Survival (PPS)

Due to the small number of progressed patients at the latest data cut of SEQUOIA informing the model (cut-off 07 of May 2021), OS and PFS data from the MURANO study were selected to inform PPS and duration of second-line treatment respectively at the PD state.[51] The model assumed that all patients progressing from a BTKi treatment were moved to a VenR regimen; therefore, six parametric survival functions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) were fitted to the VenR arm of MURANO (see Figure 4.4).[51] The exponential extrapolation was selected for the base-case based on statistical fit (as assessed using AIC and BIC, see Table 4.8). Additionally, the company did not expect “an increasing risk before general population mortality is applied” (CS, page

184).[6] The risk of mortality was constrained by age- and gender-adjusted UK general population mortality so that it never goes below the general population risk.

Table 4.8: Goodness of fit statistics for OS to model PPS – VenR (MURANO)

Distribution	MURANO (VenR) OS	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Source: CS, Table 74[6]
Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = Company submission; OS = Overall survival; PPS = Post-progression survival; VenR = Venetoclax-rituximab.

Figure 4.4 Kaplan-Meier and extrapolated survival curves for OS from the MURANO study

Source: Figure 50, CS[6]
Abbreviations: BTK = Bruton tyrosine kinase; OS = overall survival; PPS = post-progression survival.

Second-line treatment discontinuation: PFS data from MURANO was used to determine time on treatment for second-line VenR.[51] Based on statistical fit and after consultation with clinical experts who suggested a pessimistic PFS was in line with expectations for patients at this stage, the Gompertz distribution was chosen to extrapolate PFS.[6]

EAG comment: As has already been noted from NICE TA689,[64] comparing ibrutinib versus acalabrutinib, OS data from the MURANO study suffers from censoring and is highly uncertain over the long time-horizon considered in this model.[51] Therefore, the assumption of no increasing risk of death before a general population risk is applied was made under considerable uncertainty and without any clinical evidence supporting it. Furthermore, the MURANO trial centres on patients receiving second-line treatment after CIT rather than a BTKi, potentially presenting a pessimistic scenario.[51] Under the current CMA framework, this is unlikely to have a strong impact on the results but the EAG expects it could become more relevant under a CUA framework (see Sections 6.2 and 6.3). Therefore, considering the small differences in goodness-of-fit across parametric models, alternative scenarios were explored by the EAG in Section 6.2.2.

4.3.6.2 Relative efficacy

4.3.6.2.1 Zanubrutinib versus acalabrutinib in "unfit" patients

The CMA approach presented by the company is made based upon the assumption of non-inferiority, which the company argues is supported by results from the MAIC comparing pooled arm A and arm C from SEQUOIA with acalabrutinib in the ELEVATE-TN trial,[34] stating that zanubrutinib is "at least non-inferior to acalabrutinib in patients with previously untreated CLL who are unsuitable for FCR and BR therapy, irrespective of the presence of a del17pand/or TP53 mutation" (CS, page 188).[6]

As published evidence was not identified by the company looking at either the "unfit" without del17p sub-population nor the "high-risk" sub-population separately, pooled data from SEQUOIA arms A and C were adjusted to match the eligibility criteria from ELEVATE-TN.[34] Results were presented for two models in Table 4.9.

Table 4.9: Summary of MAIC results for zanubrutinib versus acalabrutinib for patients with untreated CLL

	PFS (IRC)		OS	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 48, CS[6]
Abbreviations: CLL= chronic lymphocytic leukaemia; CI = confidence interval; CS = company submission; PFS = progression free survival; IRC = independent review committee; OS = overall survival.

EAG comment: The MAIC relies on data from arm A and arm C of SEQUOIA being pooled together to generate the evidence for zanubrutinib, [redacted][44] The EAG acknowledges that lack of evidence reporting patients without del17p and/or TP53 mutation, and "high-risk" patients with del17p separately

is a key limitation which impedes carrying separate analysis for each sub-population. However, large uncertainties remain about the relative efficacy of zanubrutinib versus acalabrutinib, particularly for the "unfit" sub-population, specifically in the area of disease progression.

The uncertainty in the "unfit" sub-population is amplified by it being modelled after data from potentially "fit" patients from SEQUOIA (see Section 3.2.1.1) and the immaturity of trial data (median follow-up is approximately 22.8 months in arm A and 27.7 months in arm C) means there were very few events observed.[6]

4.3.6.2.2 Zanubrutinib versus acalabrutinib in "high-risk" patients

For the "high-risk" population, the company compared zanubrutinib with acalabrutinib across two different MAICs in patients with R/R CLL using data from ALPINE versus ELEVATE-RR or ASCEND (see Tables 4.10 and 4.11).[30,35,36] The population in these trials were deemed as a relevant proxy for "high-risk" untreated CLL patients due to the high proportion of del17p or TP53 mutation (~40%) in both trials, despite the population from all trials being R/R.[6] Results from the ELEVATE-TN MAIC could not be used to inform this subpopulation as trial results for the "high-risk" population of ELEVATE-TN were not reported independently.[34] The company also highlights TA429 and TA689 as previous appraisals with a NICE recommendation (for acalabrutinib and ibrutinib respectively), where data for patients with R/R CLL were used to model a population of patients with del17p or TP53 mutation unsuitable to receive CIT.[64,66]

Table 4.10 Summary of MAIC results for zanubrutinib versus acalabrutinib for patients with R/R CLL (ALPINE versus ELEVATE-RR)

	PFS (IRC)		PFS (INV)		OS	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 54[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CI = Confidence interval; CS = Company submission; PFS = Progression free survival; IRC = Independent review committee; INV = Investigator; OS = Overall survival; R/R = Relapsed or refractory.

Table 4.11 Summary of MAIC results for zanubrutinib versus acalabrutinib for patients with R/R CLL (ALPINE versus ASCEND)

	PFS (IRC)		OS	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]

Model 2	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 59[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CI = Confidence interval; CS = Company submission; PFS = Progression-free survival; IRC = Independent review committee; OS = Overall survival; R/R = Relapsed or refractory.

EAG comment: As with the "unfit" sub-population, the lack of evidence specific for this particular sub-population is an important source of uncertainty. Data from R/R CLL patients have been used in previous TAs as a proxy for the "high-risk" population.[64] However, the determinant factor for R/R CLL patient data to be a suitable proxy for the "high-risk" untreated population is the proportion of R/R CLL patients with del17p and/or TP53 mutation. For the ELEVATE-RR trial, 45.3% of patients had a del17p mutation and 37.4% of patients had a TP53 mutation, while for the ASCEND trial it was 18.1% and 25.2%, respectively. This makes data from these trials potentially unsuitable as a proxy for "high-risk" untreated CLL.

4.3.6.2.3 Zanubrutinib versus ibrutinib in "high-risk" patients

Due to the paucity of evidence comparing zanubrutinib with ibrutinib for previously untreated patients with del17p and/or TP53 mutation, data were used from the ALPINE trial which directly compares zanubrutinib with ibrutinib in patients with R/R CLL. An assessment of outcomes specifically on patients with del17p or TP53 mutation showed no statistically significant difference in the risk of disease progression or death using INV-assessed data (HR: [redacted], 95% CI: [redacted]) and a statistically significant reduction in the risk of disease progression or death using IRC-assessed data (HR: [redacted], 95% CI: [redacted]).

A further naïve comparison was assessed between zanubrutinib and ibrutinib in untreated "high-risk" patients using data from Mato *et al*., (2018) and arm C of the SEQUOIA trial.[5,59] Results showed no statistically significant difference in PFS (HR: [redacted]; 95% CI [redacted]), and a statistically significant reduction in OS (HR: [redacted]; 95% CI [redacted]). The results of these analyses were used to conclude that zanubrutinib is at least non-inferior to ibrutinib, which was deemed as "a conservative but clinically plausible assumption by UK clinical experts" (CS, page 190).[6]

EAG comment: The EAG considers that results from the subgroup analysis using ALPINE data in patients with del17p should be treated with caution, as they are based on a previously treated R/R population.[30] Also, only 23% of participants in ALPINE are reported as being "high-risk" (i.e., del17p and TP53 mutation is present). However, the EAG acknowledge that this might be the best available evidence. Moreover, the non-inferiority of zanubrutinib versus ibrutinib in key outcomes such as PPS and disease progression only in patients with del17p remains uncertain. Furthermore, it is unclear to the EAG whether IRC- or INV-assessed outcomes were preferred by the company, as the primary outcomes from ALPINE were INV-assessed.

The EAG advises that caution should be taken when analysing results from a naïve comparison with Mato *et al*.,(2018),[5] due to the nature of this study being retrospective, and where potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison.

4.3.7 Adverse events

Costs and disutilities associated with the different treatments to manage AEs were included in the base-case economic model. Lower grade AEs (grades 1 and 2) were not considered in the economic model and the EAG was therefore unable to assess these. The model only accounted for ≥ grade 3 treatment-

related AEs which occurred in ≥ 1% of study participants. The base-case model AEs and associated costs were applied in the first cycle of the model, hence the economic model assumed that all AEs were resolved in the first four weeks of treatment. A further assumption in the economic model was that only AEs associated with first-line treatment were included. A scenario analysis was undertaken assessing the impact of AEs on HRQoL, where utility decrements were applied to the proportion of patients experiencing the event. As above, this only applied in the first cycle of the economic model.

The AE profiles of the different treatment arms were taken from three different sources: the AE profiles of zanubrutinib were taken from SEQUOIA Cohort 1 (arm A) and Cohort 2 (arm C);[29] the AE profile of ibrutinib was taken from RESONATE-2;[31,67] and the AE profile of acalabrutinib was taken from ELEVATE-TN.[34,68] No scenario analyses were conducted in relation to the AE profiles of the different treatment arms. A summary of AEs for each of the comparators in the economic model is presented in Table 4.12.

Table 4.12: Grade ≥ 3 treatment-related AEs occurring in ≥ 1% of patients by treatment

Treatment	Zanubrutinib	Ibrutinib	Acalabrutinib
Anaemia	[redacted]	7.41%	6.70%
Thrombocytopenia	[redacted]	0.00%	2.79%
Pneumonia	[redacted]	11.85%	2.23%
Neutropenia	[redacted]	12.59%	11.17%
Hyponatremia	[redacted]	5.93%	0.00%
Hypertension	[redacted]	8.15%	3.91%
Febrile Neutropenia	[redacted]	0.00%	1.12%
Cataract	[redacted]	5.19%	0.00%
Atrial fibrillation	[redacted]	5.19%	3.91%
Source	SEQUOIA Cohort 1 and Cohort 2[6,37]	RESONATE 2[31]	ELEVATE-TN[68]

Source: CS, Table 79[6]
Abbreviations: AE = Adverse event; CS = Company submission; CSR = Clinical study report.

As the economic base-case analysis was a CMA (which makes the assumption that the effects of AEs on quality of life are the same across comparator arms), the impact of AEs on HRQoL were only explored in a scenario analysis. The CS states that a utility decrement was applied to the proportion of patients experiencing the event in the first cycle of the economic model.[6] The economic model estimated the average QALY loss due to AEs for each treatment option. This included AE rates, mean utility decrements associated with AEs and mean duration of each AE episode. The total mean QALY loss and costs of AE management were applied once at the start of the model, assuming that AEs occurred only once and were resolved in the first cycle of the model. Disutility values for the AEs included in the economic model are presented in Table 4.13.

Table 4.13: Utility decrements and duration estimates by AE

AE	Disutility	Source	Duration (days)	Source
Anaemia	-0.0900	TA487[69]	23.21	TA487[69]
Thrombocytopenia	-0.1100	TA487[69]	23.21	TA487[69]
Pneumonia	-0.1950	Tolley 2013[70]	18.20	TA359[71]

Neutropenia	-0.1630	TA487[69]	15.09	TA487[69]
Hyponatremia	-0.0200	Assumed the same as hypertension	21.00	Assumed the same as hypertension
Hypertension	-0.0200	Wehler 2018[72]	21.00	Assumption
Febrile Neutropenia	-0.1630	TA487[69]	15.09	TA487[69]
Cataract	-0.0900	Assumed the same as anaemia	23.21	Assumed the same as anaemia
Atrial fibrillation	-0.2200	Wehler 2018[72]	14	Assumption
Source: CS, Table 80[6] Abbreviations: AE = Adverse event; TA = Technology appraisal.				

Utility decrements associated with AEs were not collected as part of the SEQUOIA trial.[29] Therefore, utility decrements were sourced from previous NICE appraisals in CLL and the published literature. No scenario analyses were conducted in relation to the AE disutilities or durations.

EAG comment: The references provided in the CS for utility decrements and duration (reproduced in Table 4.13) are incorrect. In the CS, TA487 is listed as reference 59 but does not appear in the reference list of the CS and, on searching for this reference, the EAG found that the NICE guidance for this has been updated and replaced by TA796.[73] In addition, the references to support the assumptions made for all other AEs are missing (e.g. Tolley 2013 and Wehler 2018). The EAG have assumed that these references were Tolley *et al*., (2013) and Wehler *et al.,* (2018).[70,72] Given that TA487 has been replaced by TA796, it is not possible for the EAG to appraise the data in Table 4.13. On inspection of Wehler *et al*., (2018) the EAG could only find a poster presentation.[72].

The EAG consider restricting the AEs included to grade 3 and 4 only to be a strong assumption, given that some common grade 1 or grade 2 AEs may be experienced for a high proportion of patients with untreated CLL for an extended period and have an impact on patients' QoL. However, the EAG acknowledge that data on grade < 3 AEs are often not included in TAs as the data is not available. Similarly, data regarding the proportion of grade 1 and 2 AEs in each treatment arm were not reported in the CS and, therefore, the EAG were unable to investigate this further.

It was assumed that AEs occurred once within the first cycle of the model and were associated with one-off costs and disutility values, multiplied by the incidence to calculate total disutility. This assumption has been made in previous submissions to NICE.[74] The assumptions made imply that these AEs are transitory and that there are no persisting impacts on individuals over time. This assumption may be valid for certain grade 3 or 4 AEs but may not be the case for others (e.g. cataracts and hypertension). Therefore, the EAG considers that the economic model underestimated the disutilities associated with the AEs. In addition, it is unclear to the EAG why cataract AEs would be included. Based on clinical advice to the EAG, we would consider that cataracts are unlikely to be a treatment-related AE and are more likely to be age-related.

In summary, the EAG notes that several assumptions and data sources were used regarding AEs in relation to disutility values and durations. Given the issues mentioned above, it is not possible for the EAG to appraise these values. However, the EAG considers the company's approach to including AEs and associated disutility values in the economic model to be consistent with previous TAs and models of this type.[64] The EAG also recognises that the effect of AEs on the ICER is likely to be small given their low frequency, duration and utility decrements.

4.3.8 Health-related quality of life

4.3.8.1 Health-related quality of life data identified in the review

As discussed in CS Appendix D and Sections 3.1.1 and 4.1.1,[16] a single SLR was conducted which included filters to identify HRQoL studies in CLL. Thirty-three publications were identified as eligible for the HRQoL review but these were further refined by only including publications with BTKi treatments (zanubrutinib, ibrutinib and acalabrutinib). Full details were provided in the CS, Appendix H.[54] Ten eligible papers were identified: eight through the SLR and two NICE Health Technology Assessment (HTA) submissions identified through grey literature searches. Of the 10 included studies, the CS reports that nine studies were cost-effectiveness analyses (model-based) that reported HRQoL, while one further study was a literature review. The CS states that all the included studies reported utility data using the EQ-5D instrument (3L or 5L). CS Appendix H states that, of the included studies, four directly collected data on HRQoL outcomes: Osorio (2021), Cheung (2021) and Singh (2017).[54,75-77] In addition, two NICE Technology Assessment reports were identified (NICE TA689, NICE TA429), with utility values redacted.[64,66]

EAG comment: See Section 4.1 for the EAG critique on the SLR performed by the company for the untreated CLL and the R/R CLL populations. In addition to this critique, the summary of the literature provided in CS Appendix H is inaccurate. CS Appendix H states that of the studies identified: "four collected data on HRQoL outcomes".[54] Only three papers are cited and one was cited in error, as it was a literature review. On review of the included studies presented in the CS and Appendix H,[6,54] the EAG found that the three studies that directly collected HRQoL data were: Osario (2021) using the EQ-5D-5L (value set not reported); Barr (2018) using EQ-5D-5L (value set not reported)[78]; and Cheung (2021) using EQ-5D-5L in a Canadian population (Canadian EQ-5D-5L value set).[75,76]

The EAG recognises that the company used a range of databases and searches of the grey literature to identify relevant literature in HRQoL. However, the EAG still have some concerns that the company's search may not have been sensitive enough to identify all relevant papers (see Section 4.1). Overall, the EAG considers that a separate SLR on HRQoL should have been undertaken. As a separate targeted SLR was not undertaken, the EAG cannot be confident that all relevant literature was identified.

4.3.8.2 Health state utility values

A CUA was undertaken as a scenario analysis only (see Section 4.3.2 and Section 5.1.3). The CS provides HRQoL data collected from the SEQUOIA trial.[6,29] Data were collected using EQ-5D-5L administered at baseline and then every 12 weeks from the start of cycle 1 for 96 weeks and then every 24 weeks until disease progression. Utility values were generated by mapping the EQ-5D-5L data to the EQ-5D-3L using a cross-walk algorithm and analysed using mixed-effect linear regression with a random intercept and adjusted for baseline utility (mean value of eligible population).[19,79] The CS states that as there was no evidence of systematic differences in HRQoL across study arms. Utility values were pooled across arm A and Arm B of the trial.

EAG comment: As the utility data for the EQ-5D-5L were only presented graphically in the CS, the EAG requested that the company provide descriptive summaries (mean and measure of variance) of the EQ-5D-5L utility data for each time point data were collected.[6] The company provided data from baseline to week 144 presented in Table 4.14.[12] The EAG is satisfied that there are no meaningful differences in EQ-5D-5L scores between zanubrutinib or BR from SEQUOIA Cohort 1. However, as reported in Section 3.2.15, PROs were only assessed in Cohort 1 of SEQUOIA. Therefore, the EAG cannot comment on HRQoL for Cohort 2; this has an implication for the economic analysis, as utilities for the untreated "high-risk" population are not available.

The EAG also note that the utility values reported from SEQUOIA have been derived using linear mixed models (with repeated measures), which assume the normality of residuals. EQ-5D utility data are known to have a non-normal distribution. Therefore, alternative models, such as the adjusted limited dependent variable mixture model may have been more appropriate to analyse these data.[80] There is no evidence in the CS that other model types were applied to account for the probable non-normality in the EQ-5D data.[6] The EAG note that the impact of using alternative model types on the utility values, and therefore the overall results, is likely to be small.

Table 4.14: Descriptive summaries of EQ-5D-5L data in SEQUOIA

	Zanubrutinib (N=225)		**BR (N=195)**	
Assessment	**Mean (SD)**	**95% CI**	**Mean (SD)**	**95% CI**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 1	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 12	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 24	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 36	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 48	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 60	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 72	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 84	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 96	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 120	[redacted]	[redacted]	[redacted]	[redacted]
RA - WEEK 144	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to clarification letter[12]
Abbreviations: BR = Bendamustine-rituximab; CI = Confidence interval; RA = Response assessment; SD = Standard deviation.

The CS presented data on the predicted utility for the health states included in the economic model (PF and PD) in comparison to age-sex general population matched utilities. This was incorrectly referenced in the CS, Table 77[6] and the EAG has assumed this to be Ara *et al*.,(2011)[81]; see Table 4.15.[81] Given the data for PF and PD were higher than the UK general population data, the CS states that the data from the SEQUOIA trial lacked face validity.[6]

Table 4.15: Utility Model Including Progression Status as Predictors

Predictor	No. of Patients	No. of Obs.	Coefficient (95% CI)	Source
Predicted utility for health states				
PF	[redacted]	[redacted]	[redacted]	SEQUIOA
PD	[redacted]	[redacted]	[redacted]	
Mean utility based on published general population in UK				
General population irrespective of health status (65 to ≤ 70)			0.804 (0.790, 0.817)	Ara and Brazier 2011;[81] supplementary Table A4
General population with health condition "cancer" (65 to ≤ 70)			0.730 (0.652, 0.807)	
General population without health condition "cancer" (65 to ≤ 70)			0.808 (0.794, 0.821)	

Source: CS, Table 77[6]
*5 out of 420 eligible patients were removed from the analysis due to missing progression status. It wasn't clear to the EAG in the CS what the * was referring to in Table 77.
Abbreviations: CI = confidence interval; PD = progressed disease; PF = progression-free; UK = United Kingdom.

For the cost-utility scenario analysis, the company used published utility values identified in the SLR (specifically, NICE TA689).[64] Utility values for PF and PD in the economic model were based on the values accepted by NICE in TA689.[64] The CS states that, in TA689, a PF utility of 0.783 and PD of 0.6 were accepted.[64] The CS states that the PF utility value was generated using EQ-5D (version not stated) for the age and gender matched general population.[6] The CS states that PD utility values were informed by Holzner *et al*., (2004),[82] where QoL was measured using EORTC QLQ-C30 and Functional Assessment of Cancer Therapy (FACT) general questionnaire in a sample of 418 cancer patients, of which 81 had CLL. The CS submission does not expand on the data time-points collected or methods of analysis. Table 4.16 presents a summary of the values used in the cost-utility scenario analysis.

Table 4.16 Summary of utility values for cost-utility scenario analysis

State	Utility value: mean (standard error)	95% CI	Sourced
PF	0.783 (0.0064)	0.770, 0.795	EQ-5D score for the age- and sex-matched general population, based on the EAG preferred value in NICE TA689[64]
PD	0.600 (0.0597)	0.481, 0.714	Holzner et al (2004)[82]

Source: CS, Table 81[6]
Abbreviations: CI = Confidence interval; CS = Company submission; EAG = Evidence Assessment Group; NICE = National Institute of Health and Care Excellence; PD = Progressed disease; PF = Progression-free.

EAG comment: The PD values used in the economic model were informed by Holzner *et al*., (2004).[82] The EAG has found errors in the reporting of the evidence from this source. The CS states that, in Holzner *et al*.,(2004),[82] HRQoL was measured using the EORTC QLQ-C30 and the FACT general questionnaire in 418 cancer patients, 81 of whom had CLL. On inspection of this paper, 97 patients diagnosed with CLL were asked to participate in this study (Innsbruck, Austria) and were sent a sociodemographic questionnaire and the EORTC QLQ-C30.[82] Seventy-six of these patients responded and were included in the analysis; there is no reference to FACT or related data in this paper.[82]

In the scenario analysis, the company assumed that overall utilities were appropriate to be applied to all treatment arms, instead of using treatment-specific utilities.[6] The EAG considers that different utility values should have been used for different treatment arms and the imprecision explored in sensitivity analyses. The CS states that a PD utility value of 0.60 has been accepted in a previous TA(TA689).[6] The EAG note that, although this assumption may have been used previously, this is not sufficient justification for its use here.

Overall, the EAG considers the HSUVs used in the economic model to be associated with a high degree of uncertainty. This is due to a lack of validity in trial data, limited data from elsewhere and use of overall rather than treatment-specific utilities either from trial data or the literature. In addition, the EAG considers that data from SEQUOIA should have been used in a sensitivity analysis to assess the uncertainty and its implications for the results of the CUA.

4.3.9 Resources and costs

The price year of the economic analysis was not provided in the CS. This was requested by the EAG and confirmed by the company in response to the clarification letter to be 2020/2021.[12] All costs presented for both the untreated CLL and R/R CLL economic models are in this price year unless otherwise stated.

4.3.9.1 Resource use and costs data identified in the review

According to CS Appendix I,[55] of 113 studies that met the inclusion criteria for cost and resource use, the SLR identified three eligible studies from UK perspective and two NICE appraisals for patients with previously untreated CLL.

Of three studies included,[83-85] two[83,84] were cost-effectiveness studies which both used a 3-state semi-Markov model. These studies did not report data on resource use. An early economic evaluation reported resource use by health state (PF and PD).[85] All three studies reported treatment costs, including drug administration and acquisition and AE costs.[83-85]

The two NICE appraisals (TA689, TA429) identified each developed a 3-state partitioned survival model for a R/R CLL population from a UK NHS and PSS perspective.[64,66] They reported treatment costs, disease management costs and AE costs.[64,66]

EAG comment: The company performed a single SLR to search several databases and other literature sources (see Sections 3.1.1, 3.1.3 and 4.1.1) and the company relied only on this single SLR to identify all cost-effectiveness, HRQoL and cost and resource use data. As described in Section 4.1 there are limitations with this review. Of the studies identified, one, Munir *et al*.,(2020),[83] was only available in abstract form only and hence did not contain all of the information needed to populate the economic model.

4.3.9.2 Intervention and comparator drug costs

The company combined unit costs from the British National Formulary (BNF) with dosing regimens (see Section 4.3.4) to estimate the total drug costs.[63]

4.3.9.2.1 Dose, vial sharing and dose intensity

In the base-case analysis, treatment with a BTKi was given until disease progression; alternative treatment duration assumptions were explored in scenario analyses.[6] Given than the company used the MURANO study to model PPS and duration of subsequent treatments, it was assumed that all patients received subsequent treatment with VenR.[6,51]

Wastage in the base-case analysis was only considered for IV drugs dependent on BSA (i.e., rituximab). The company assumed a BSA of 1.92 $m^{2,}$ based on the SEQUOIA trial.[6] For all treatments a relative dosing intensity of 100% was assumed.[6]

EAG comment: The details of how BSA was calculated were not provided in the CS but were subsequently provided following a request by the EAG.[12] The EAG considered the method of calculation appropriate. From the information provided in the CS it was unclear to the EAG how wastage was considered in the economic model. Furthermore, there could also be wastage costs associated with oral drugs for patients who die without completing their full course of treatment, these costs were not considered in the economic model. However, the EAG notes that under the assumption of equivalent clinical effects on survival, this cost would have no effect on the CS base-case results.

4.3.9.2.2 Acquisition costs

Drug acquisition costs were dependent on the dosing regimens of the three treatments (zanubrutinib, acalabrutinib and ibrutinib) and subsequent treatment (VenR).[6] The package price and price per cycle of each of the treatments (first and second line) are presented in Table 4.17. Of note is that the costs of zanubrutinib were based on the confidential PAS price.

Table 4.17: Drug package price and price per cycle and costs

Treatment	Dose strength	Pack Size/Vial Volume	Administration route	Cost per Pack £	Cost per cycle £
Zanubrutinib	80 mg	120	Oral	[redacted]	[redacted]
Acalabrutinib	100 mg	60	Oral	5,059.00	4,721.73
Ibrutinib	420 mg	28	Oral	4,292.40	4,292.40
Venetoclax (subsequent treatment only)	100 mg	7	Oral	299.34	Cycle 1: 1,107.56 Cycles 2-26: 4,789.44
Rituximab (subsequent treatment only)	10 mg/ml 10 mg/ml 120 mg/ml	10 ml 50 ml 12 ml	IV	157.17 785.84 1,344.65	Cycle 1: 1,198.56 Cycle 2-6: 1,339.28

Source: CS, Table 83[6]
Abbreviations: CS = Company submission; IV = Intravenous; mg = Miligram; ml = Mililitre.

EAG comment: The CS states that "relative dosing intensity (RDI) is assumed to be 100% for all treatments" (CS, Section B.3a.5.1, Page 200) and refers to TA689 to support this assumption.[6,64] The EAG notes that in TA689, data provided by the company did not show 100% RDI. The EAG assessing the company submission for TA689[64] had previously raised the concern that assuming 100% RDI would consequently lead to overestimation of acquisition costs, therefore this concern also applies for the current CS.

4.3.9.2.3 Administration costs

Drug administration costs were only applied to rituximab, an IV drug, and not considered for oral medications. Administration costs varied between initial and subsequent treatment.

Table 4.18: Drug administration costs

Description of cost	Use in model	Unit cost (£)	Source
Deliver Complex Chemotherapy , including Prolonged Infusion Treatment, at First Attendance	Rituximab: one administration within Cycle 1	526.52	National Schedule of NHS Costs 2020/21[86]
Deliver Subsequent Elements of a Chemotherapy Cycle	Rituximab: one administration per cycle for Cycles 2-6	470.62	National Schedule of NHS Costs 2020/21[86]
Source: CS, Table 84[6] Abbreviations: CS = Company submission; NHS = National Health Service.			

EAG comment: The EAG have no concerns in how drug administration costs were estimated.

4.3.9.3 Monitoring and disease management costs

A one-time monitoring cost for venetoclax was applied at treatment initiation in the company model. This cost was associated with laboratory tumour lysis syndrome (TLS) prophylaxis, which was required for all patients prior to initiation of venetoclax treatment. This monitoring cost was calculated using the TLS risk distribution and estimated a TLS prophylaxis cost for each of the risk categories.[6] The MURANO trial was used to determine the TLS risk category proportions and costs were obtained from TA561 (Table 4.19).[3,9]

Table 4.19: TLS management costs

Risk category	Proportion	Cost (£)
Low	17.53%	1,430.40
Intermediate	54.64%	2,016.54
High	27.84%	2,146.81
Total		1,950.08
Source	MURANO trial[9]	NICE TA561[3]
Source: CS, Table 87[6] Abbreviations: NICE = National Institute of Health and Care Excellence; TA = Technology appraisal; TLS = Tumour lysis syndrome.		

EAG comment: The company obtained the risk categories from the MURANO trial[9] which EAG agree was an appropriate source as this trial is representative of the UK population. Associated unit costs were

taken from NICE TA561,[3] which was published in 2019. The costs of TLS management presented in the CS document and the economic model were not inflated to the price year 2021.

4.3.9.4 Adverse effects costs

As previously discussed in Section 4.3.7, all grade ≥ 3 treatment-related AEs occurring in ≥ 1% of participants receiving BTKi treatment in were included in the company model. Total AE costs were calculated based on the proportion of AE incidences for each of the BTKi treatments (see Table 4.12) and the unit costs in Table 4.20.

Table 4.20: AE management costs

Adverse event	Cost (£)	Source	Comment
Anaemia	721.99	National Schedule of NHS Costs 2020/21[86]	SA09 Other Red Blood Cell Disorders with CC Score 0-5, non-elective short stay
Thrombocytopenia	881.88	National Schedule of NHS Costs 2020/21[86]	SA12 Thrombocytopenia, non-elective short stay
Pneumonia	782.27	National Schedule of NHS Costs 2020/21[86]	DZ11 Lobar, Atypical or Viral Pneumonia, non-elective short stay
Neutropenia	761.01	National Schedule of NHS Costs 2020/21[86]	SA35 Agranulocytosis, non-elective short stay
Hyponatremia	518.83	National Schedule of NHS Costs 2020/21[86]	KC04 Inborn Errors of Metabolism, score 0-2 non-elective short stay
Hypertension	537.86	National Schedule of NHS Costs 2020/21[86]	EB04Z Hypertension, non-elective short stay
Febrile Neutropenia	2,719.97	National Schedule of NHS Costs 2020/21[86]	SA35 Agranulocytosis, non-elective short stay and long stay
Cataract	1,821.35	National Schedule of NHS Costs 2020/21[86]	BZ32-BZ34, non-elective short stay and long stay
Atrial fibrillation	782.27	National Schedule of NHS Costs 2020/21[86]	Assume the same as infection (DZ11)

Source: CS, Table 86[6]
Abbreviations: AE = Adverse event; CC = Complication and comorbidity; CS = Company submission; NHS = National Health Service.

EAG comment: The EAG doesn't have any concerns about the unit costs used by the company. However, the same concerns raised about the inclusion and duration of AEs raised in Section 4.3.7 apply here.

4.3.9.5 Health state costs

Three health states were defined in the model: PF, PD and dead. The costs of drug acquisition and drug administration were applied in all states dependent on the treatment arms.[6] The company stated that: "costs related to routine follow-up and disease management included in the model were calculated through a micro-costing approach where resource use was multiplied by the unit cost for each resource item" (CS, page 201).[6]

The company used NICE TA689 to identify resource use frequencies for both the PF and PD health states.[64] Unit costs were obtained from the NHS National Schedule of Costs 2020/21.[86] Based on clinical advice received by the company the costs associated with transfusion burden were omitted as these costs were more specific to patients receiving CIT.[6] They also advised that radiological assessments, such as CT scans, had replaced chest x-rays, hence only costs associated with CT scans were considered in the economic model.[6] The resources and costs assigned to routine follow-up and disease management are presented in Table 4.21.

Table 4.21: Medical resource unit costs and frequencies

Resource item	Costs		Resource use per cycle		
	Unit (£)	Source	PF state	PD state	Source
Full blood count	3.63	National Schedule of NHS Costs 2020/21[86]	0.31	0.61	NICE TA689[64]
Lactate dehydrogenase	1.85	National Schedule of NHS Costs 2020/21[86]	0.23	0	NICE TA689[64]
Haematologist visits	157.89	National Schedule of NHS Costs 2020/21[86]	0.15	0.46	NICE TA689[64]
CT scan	105.66	National Schedule of NHS Costs 2020/21[86]	0	0.15	NICE TA689[64] Clinical expert opinion
Bone marrow exam	574.44	National Schedule of NHS Costs 2020/21[86]	0	0.08	NICE TA689[64]
Inpatient visit (non-surgical)	750.17	National Schedule of NHS Costs 2020/21[86]	0	0.31	NICE TA689[64]
Aggregated cost per cycle			**£25.23**	**£369.20**	

Source: CS, Table 85[6]
Abbreviations: CS = company submission; CT = Computerised tomography; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = Progressed disease; PF = Progression-free.

EAG comment: The company noted in the CS that a micro-costing approach was used to estimate the monitoring and disease management costs.[6] However, this is not the approach that was used. Unit costs were extracted from the NHS Schedule of Costing and combined with healthcare services informed by the literature for both the PF and PD health states.[86] The EAG had no further concerns on the assumptions made by the company to estimate costs associated with resource use for each health state.

4.3.9.6 Terminal care costs

A terminal care cost of £7,000.72 was assigned to each death as a one-off cost in the economic model. This cost came from Round *et al*., (2015),[87] which estimated the direct and indirect costs for end of life care for lung, breast, colorectal and prostate cancer in England and Wales.[87]

EAG comment: The EAG is uncertain about the applicability of the terminal care cost from Round *et al*., (2015) to patients in the untreated CLL model, given that haematological cancers were not included in the study population.[87] However, the EAG acknowledge that the costs associated with end of life care may not differ greatly based on cancer diagnosis and given that the same cost was applied to all treatments. Thus, the EAG consider that it is unlikely that any uncertainty in these costs will have a big impact on the results of the economic model. Although Round *et al*., published in 2015 following

information provided in the company response to the clarification letter[12] the EAG has no concerns with how these costs were inflated.

4.3.10 Summary of company assumptions applied in base-case analysis

The company analyses the cost-effectiveness of zanubrutinib versus ibrutinib or acalabrutinib using a CMA approach, assuming equivalent effectiveness in terms of survival and quality of life across treatment and comparator arms. The justification of the CMA approach was founded on the results obtained from the MAIC analyses comparing data from SEQUOIA[29] and ELEVATE TN[34] for the untreated population, and ALPINE[88] with either ELEVATE-RR[36] or ASCEND[35] for the R/R population, to demonstrate non-inferiority of zanubrutinib versus acalabrutinib on key survival outcomes.

The EAG considers that the MAIC analyses do not present sufficient evidence of non-inferiority, and instead present no evidence of a difference due to limited data and estimate imprecision. Henceforth, the EAG does not consider a CMA to be the best approach to represent the decision problem the decision problem. The EAG acknowledges the adoption of a CUA as the company's base-case may not have changed the conclusions, as illustrated by the CUAs undertaken by both the company, in scenario analyses (see Section 5.1.1.2) and the EAG in their base-case analysis (see Section 6.2.1). However, the EAG cannot be certain of these conclusions due to limitations with the modelling associated with applying a CUA to this economic model (see Section 4.3.2.1). The EAG attempted to address this uncertainty by considering alternative assumptions which maximised all the data available and arguably produced more robust estimates of cost-effectiveness (see Section 6.2.1.2).

Table 4.22 summaries the assumptions made by the company in their base-case economic model in untreated CLL.

Table 4.22: Summary of company assumptions applied in the base-case analysis for untreated CLL

Parameter	Details	Section	Source
Population	Untreated CLL with pooled arm A (without del17p) and arm C (with del17p) from SEQUOIA	Section 4.3.3	SEQUOIA trial[59]
Perspective	Payer (NHS England and PSS)	Section 4.3.5	Assumption
Time horizon	Lifetime (30 years)	Section 4.3.5	Assumption
Proportion females	[redacted]	Section 4.3.3	SEQUOIA trial[59]
Starting age	[redacted]	Section 4.3.3	SEQUOIA trial[59]
BSA	1.92 m^2	Section 4.3.3	SEQUOIA trial[59]
Half-cycle correction	Yes	Section 4.3.2	Assumption
Discount rate	0.035	Section 4.3.5	NICE guidelines[19]
Survival models			
TTP distribution	Generalised Gamma	Section 4.3.6.1.1	Based on pooled arm A and arm C data from the SEQUOIA trial[59]

PrePS distribution	Generalised Gamma	Section 4.3.6.1.2	Based on pooled arm A, arm B, and arm C data from the SEQUOIA trial[59]
PPS distribution	Exponential	Section 4.3.6.1.3	Based on the MURANO trial[51]
PFS 2L distribution	Gompertz	Section 4.3.6.1.4	Based on the MURANO trial[51]
Hazard ratios			
TTP zanubrutinib vs acalabrutinib	1	Section 4.3.6.2	CMA assumption
TTP zanubrutinib vs ibrutinib	1		
PrePS zanubrutinib vs acalabrutinib	1		
PrePS zanubrutinib vs ibrutinib	1		
AE incidence			
Zanubrutinib	Grade ≥ 3 occurring in > 1% of patients	Section 4.3.7	Pooled arm A and arm C data from the SEQUOIA trial[59]
Acalabrutinib			RESONATE-2[31]
Ibrutinib			ELEVATE-TN[68]
Utility values			
PF	0.783	Section 4.3.8	NICE TA 689[64]
PD	0.6		Holzner et al. 2004[82]
Costs and resource use			
Resource use	Resource use from the literature	Section 4.3.9	NICE TA 689[64]
End of life costs	Resource use and costs from the literature		Round 2015[87]
TSL management costs	One-time monitoring for venetoclax		Seymour 2018[9] and NICE TA561[3]
Treatment acquisition	PAS discount applied to zanubrutinib		BNF,[63] company data
Treatment duration	Until progression or death	Section 4.3.4	Assumption
Subsequent treatment	VenR	Section 4.3.9	BSH guidelines[2]

Source: Created by the EAG based on CS, Table 89[6]
Abbreviations: 2L = Second-line therapy; AE = Adverse event; BNF = British National Formulary; BSA = Body surface area; BSH = British Society for Haematology; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PAS = Patient access scheme; PD = Progressed disease; PF = Progression-free; PFS = Progression-free survival; PPS = Post-progression survival; PrePS = Pre-progression survival; PSS = Personal Social Services; TSL = Tumour lysis syndrome prophylaxis; TTP = Time to progression; VenR = Venetoclax-rituximab.

4.4 Summary of cost effectiveness analysis for the R/R population

The company did not identify any previous economic evaluations of zanubrutinib in patients with R/R CLL. Previous TAs in CLL were used to justify the key features of a de novo model.[6] Like the untreated CLL economic model, a CMA was used to assess the cost-effectiveness of zanubrutinib compared with acalabrutinib and ibrutinib in patients with R/R CLL. Thus, the company assumed no clinical difference between zanubrutinib, acalabrutinib, and ibrutinib whilst estimating the differences in their cost. This choice was based on the results from the ALPINE trial and the MAIC analyses (see Sections 3.2.2 and 3.3.2).

4.4.1 EAG comment on company's review of cost-effectiveness evidence

See Section 4.1 for the EAG critique on the SLR performed by the company for the untreated CLL and R/R CLL populations.

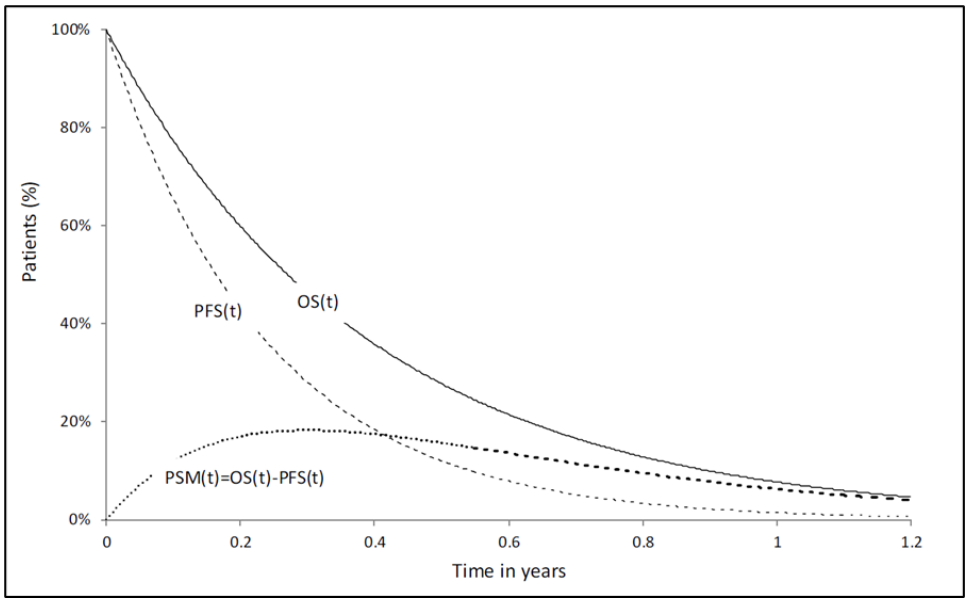
4.4.2 Model structure

The model structure presented for the R/R CLL population was different from the untreated CLL population (see Section 4.2.2), as instead of a semi-Markov approach, the company presented a partitioned survival model (PSM) for the disease pathway of R/R CLL patients.

4.4.2.1 Health states/events and transitions

The partitioned survival approach used to model R/R CLL consisted of three independent and mutually exclusive health states: PF, PD and death. All patients started in the PF health state and received treatment until either disease progression or death. State occupancy in the PF state was defined using the PFS curve for each treatment and was constrained by the OS curve. The occupancy in the PD state was defined by the difference between the parametric extrapolation of the OS curve and the PFS curve (see Figure 4.5).

Figure 4.5: Illustration of state occupancy in a partitioned survival model



Source: CS, Figure 58[6]
Abbreviations: OS = Overall survival; PFS = Progression-Free Survival; PSM = Partitioned Survival Model; t = Time.

State occupancy:

- In the PF health state, patients received treatment prior to either progression or death. The PFS(t) curve shown in Figure 4.5 represents the proportion of patients in the PF health state at time t and was constrained by OS(t) to prevent survival curves from crossing each other. Consequently, the number of people who are PF cannot be greater than the total number of patients who are alive. PFS data in the model was derived directly from INV-assessed patient data from the ALPINE trial.[30]
- Patients in the PD health state have progressed disease and moved on the next line of treatment. The company calculated the proportion of patients who were alive but not PF (PD at time t) by subtracting PFS(t) from OS(t) (see Figure 4.5).
- Death was modelled as an absorbing health state. The proportion of patients in this health state was calculated as 1-OS(t) (see Figure 4.5). OS data in the model was derived directly using INV-assessed patient data from the APINE trial.[30]

EAG comment: The EAG considers the 3-health state partitioned survival structure used by the company to be appropriate for the R/R CLL population. However, further justification on the choice of model used, beyond being based on the models used in previous TAs, was needed by the company.[19] The EAG acknowledge that the paucity of data in this population was a limitation in developing a more sophisticated model to better represent the disease pathway but this needed further discussion by the company.

4.4.3 Population

The population were adult patients with R/R CLL who had at least one previous systemic therapy. The mean age of the modelled population was [redacted] years. This population had a mean weight of [redacted]. The BSA for the modelled population was calculated as 1.92 m^2. Nearly a third ([redacted]) of this population were assumed to be female. Baseline characteristics that were used in the model were taken from the ALPINE trial.[30]

EAG comment: The EAG considers the population characteristics used in the model to be appropriate.

4.4.4 Interventions and comparators

The intervention for the R/R CLL model was zanubrutinib, as described in Section 4.3.4. The comparators in the R/R CLL model were ibrutinib and acalabrutinib, with dosing regimens equivalent to those described in Section 4.3.4 for the "high-risk" untreated CLL population.

The costs of subsequent treatments were included in the R/R CLL model. However, they were modelled differently to the approach adopted for the untreated CLL population, as the proportion of patients receiving VenR was assumed to be 80% with the remaining 20% receiving an idelalisib-rituximab combination.[6] In current practice, idelalisib is administered until disease progression or unacceptable toxicity. In the company model, idelalisib is administered to patients in the PD state from entry until death occurs. The same assumptions for subsequent treatments are applied across the intervention and comparator arms.

EAG comment: The EAG considers acalabrutinib and ibrutinib to be appropriate comparators for the R/R CLL population. However, the EAG considers the exclusion of VenR as a relevant comparator to be a potential deviation from the NICE scope, as patients with a prior line of therapy with CIT would be eligible to either BTKi or VenR (see Section 2.3).

The EAG considers that the 20% proportion of patients being treated with an idelalisib combination to be too high for NHS clinical practice, as this is a rarely used treatment. Instead, the EAG considers a 5% proportion to be more representative of current practice, based on advice received from the clinical expert consulted. Under the company base-case CMA framework, this is expected to have no impact on cost-effectiveness results. However, under a CUA framework the EAG expects this to have an impact potentially at increasing the cost of subsequent treatments for patients progressing. This is explored as an EAG scenario in Section 6.3.2.

4.4.5 Perspective, time horizon and discounting

The analysis took an NHS and PSS perspective, using a lifetime horizon (30 years) and a 3.5% discount rate (see Section 4.2.5).

EAG comment: The EAG considers the perspective and discount rate used in this model to be appropriate.

4.4.6 Treatment effectiveness and extrapolation

The company conducted a time to event analysis for the R/R CLL population based on patient-level survival data from the ALPINE trial.[30] PFS was derived directly from INV-assessed IPD from the ALPINE trial.[30] OS was derived directly from projected Kaplan-Meier data reported in the ALPINE trial.[30] The company's base-case model assumed that all BTKis were given until progression, in line with the respective SmPCs.

Under the CMA approach, clinical effectiveness was assumed to be the same across all treatment arms. Therefore, the parametric survival curves obtained from the zanubrutinib arm in ALPINE were applied to all comparator arms. The CMA approach was argued to be justified by the company from the results of relative efficacy between zanubrutinib compared with acalabrutinib across two MAICs (see Section 3.3.2) and zanubrutinib compared with ibrutinib using head-to-head trial data from ALPINE.[30] Details of the approach presented in the CS of the methods used to select a parametric extrapolation and the evidence used to justify a CMA, along with their respective EAG critique are presented in Section 4.4.6.1 and Section 4.4.6.2.

4.4.6.1 Survival analysis and extrapolation methods

Time to event analysis: NICE DSU technical support document 14 was used by the company as their framework to perform their survival analysis.[89] Kaplan-Meier data were fit across six parametric distributions to predict survival over the modelled time horizon: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma. According to the CS, clinical expert opinion, comparisons with real word data and the assessment of statistical fit measures were used to assess clinical plausibility in line with the NICE DSU document.[89] Kaplan-Meier data from the ALPINE trial were used as a reference, upon which the extrapolated parametric survival curves were visually compared against data from the ALPINE trial.[30] The parametric survival curves used for the company base-case were meant to be selected based on clinical plausibility and statistical fit to the trial data.

EAG comment: Clinical plausibility has a very important role in the selection of the most appropriate parametric curves used to predict survival. The EAG considers that insufficient details were provided in the CS about how the opinions of the clinical experts were elicited, nor on the information that they were presented with. Further information was sought by the EAG during the clarification stage. In response, the company provided the EAG with the report of the advisory board meeting held with the clinical experts.[44] The EAG still had some concerns about the justification of the survival models chosen by the company and explored uncertainty in these assumptions in scenario analyses (see Section 6.3.2)

4.4.6.1.1 Progression Free Survival (PFS)

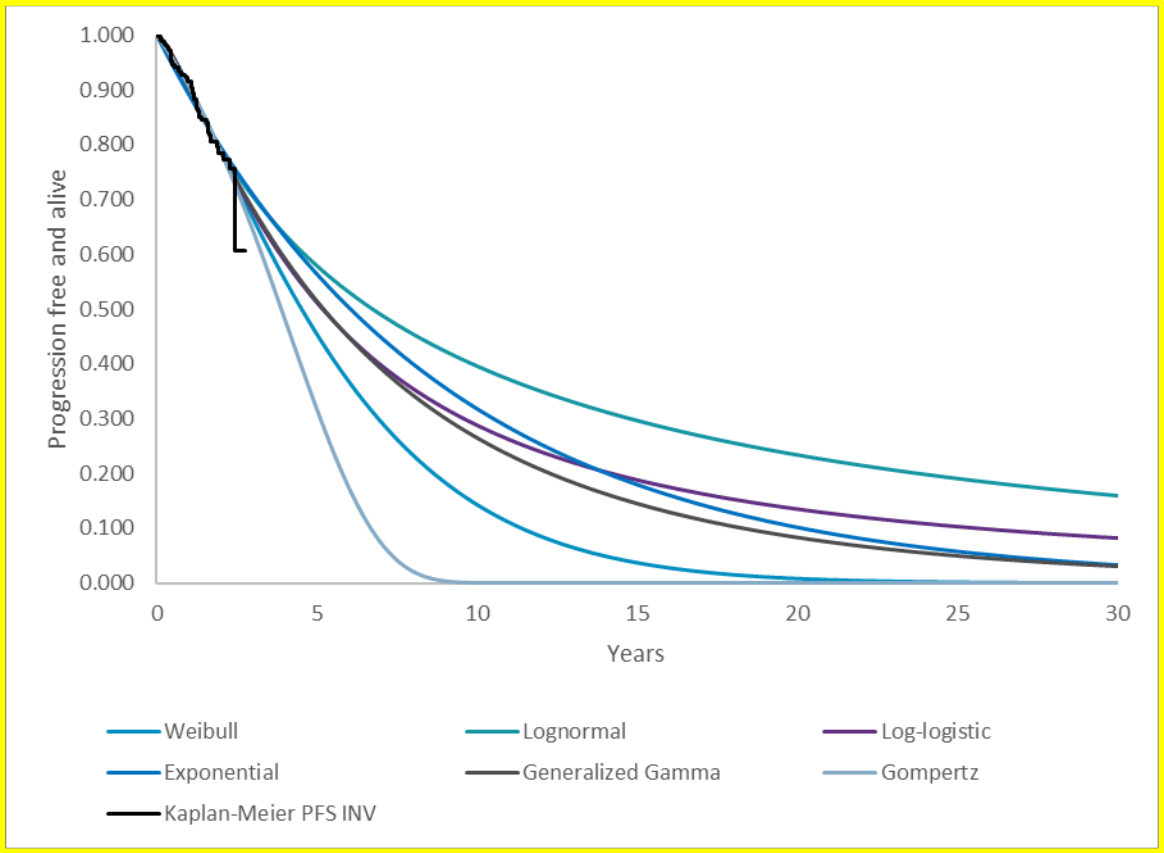
In the company model, base-case extrapolations of PFS were based on the INV-assessed results from the ALPINE trial.[30] The scenario analyses considered the impact of using IRC-assessed outcomes to model PFS. The log-logistic distribution gave the best statistical fit (AIC) to the observed data for zanubrutinib, with Weibull providing the second-best statistical fit (AIC, see Table 4.23). The CS reports that, for the INV-assessed PFS for zanubrutinib, the most conservative estimates were provided by the Gompertz model, followed by the Weibull model (see Figure 4.6).

Table 4.23: Goodness-of-fit statistics for INV- assessed PFS – zanubrutinib (ALPINE)

Distribution	Zanubrutinib (stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Source: CS, Table 102[6]
Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CS = Company submission; INV = Investigator; PFS = Progression-free survival.

Figure 4.6: INV-assessed PFS with extrapolated parametric survival curves – zanubrutinib (ALPINE)



Source: CS, Figure 59[6]
Abbreviations: INV = Investigator; PFS = Progression-free survival.

Clinical opinion sought by the company suggested that "~50% of patients would be progression free at 50 months" (CS, page 233),([6 with similar results reported from the ASCEND trial (62% progression free at 42 months) and RESONATE trial (median of 44.1 months).[31,35] Table 4.24 displays the landmark INV-assessed PFS rates for zanubrutinib. The company selected the Weibull distribution, which produced extrapolations at which 50% of patients were progression free at 4.52 years, to inform PFS in their base-case. The Gompertz curve provided the second closest estimation of median PFS and was therefore used in the company's sensitivity analysis (see Section 5.1.3).

Table 4.24: Landmark INV-assessed PFS – zanubrutinib (ALPINE)

Distribution	Median (months)	PFS (%) at landmark timepoints*					
		1-year	5-year	10-year	15-year	20-year	30-year
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 103[6]
*Using generalised gamma OS to ensure PFS was not capped by OS.
Abbreviations: INV = Investigator; OS = Overall survival; PFS = Progression-free survival.

EAG comment: It is not clear to the EAG why the BIC coefficient was not mentioned during the assessment of statistical fit. Nevertheless, the coefficients reported show very small differences in statistical fit across the models assessed. This increases the role of external data and clinical expert opinion to select the most appropriate parametric distribution. The comparisons with the literature presented by the company draw upon studies that have a follow-up of less than five years, this leaves uncertainty over longer term estimates. Clinical opinion sought by the EAG considered the predictions from the Weibull model to present a rather pessimistic scenario of PFS over the long-term. Therefore, the EAG considers that more optimistic assumptions should be assessed, scenarios with more optimistic PFS were explored on the EAG analyses in Section 6.3.2.

4.4.6.1.2 Overall Survival (OS)

The company's OS projections were directly based on the Kaplan-Meier data from the ALPINE trial.[30] The 01 December 2021 data cut-off from ALPINE was used to derive PFS and OS parametric extrapolations from the respective patient data. The exponential distribution provided the best statistical fit (AIC) and the log-normal distribution provided the second best statistical fit (AIC; see Table 4.25). The company considered all distributions to have a reasonably close statistical fit.

Table 4.25: Goodness of fit statistics for zanubrutinib (ALPINE)

Distribution	Zanubrutinib (Stratified)

	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Source: CS, Table 104[6]
Abbreviation: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CS = Company submission; OS = Overall survival.

Figure 4.7 displays the parametric survival extrapolations for OS for zanubrutinib. The CS stated that the Weibull distribution provided the most conservative prediction.[6]

Figure 4.7: INV-assessed OS with extrapolated parametric survival curves – zanubrutinib (ALPINE)

[redacted]

Source: CS, Figure 60[6]
Abbreviations: INV = Investigator; OS = Overall survival.

Clinical expert opinion sought by the company suggested that: "~50% of patients would be expected to be alive at 10 years" (CS, page 235).[6] Table 4.26 displays landmark OS rates used for the model. The

company selected the Weibull distribution to inform the OS extrapolation in the base-case; this selection was justified by the company as the predictions were closer to the expert opinion consulted.[6]

Table 4.26: Landmark OS – zanubrutinib (ALPINE)

Distribution	Median (months)	OS (%) at landmark timepoints					
		1-year	5-year	10-year	15-year	20-year	30-year
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 105[6]
Abbreviations: OS = Overall survival.

EAG comment: As with the extrapolation of PFS over the long-term presented previously (see Section 4.4.6.1.1), the EAG have concerns with the selection process used by the company, whereby BIC estimates were not part of the discussion of statistical fit and the selection of the parametric distribution was strongly reliant on clinical expert opinion.

4.4.6.1.3 Second-line treatment duration:

In the model base-case, the company assumed that all BTKis were administered until progression, in line with respective SmPCs. This assumption was based on advice received from clinical experts.[6] In the company's sensitivity analysis, an alternative approach of modelling extrapolated TTTD data from ALPINE data for zanubrutinib and ibrutinib was investigated[6] The company did not explore alternative approaches for acalabrutinib due to the absence of corresponding TTTD data.

EAG comment: The EAG has no concerns surrounding the company's assumptions about treatment duration.

4.4.6.2 Relative efficacy

4.4.6.2.1 Zanubrutinib versus acalabrutinib

The company assumed zanubrutinib was at least non-inferior to acalabrutinib in patients with R/R CLL.[6] This assumption was based on the HR and 95% CIs of PFS and OS extracted from two MAICs; one using data from ELEVATE–RR and one using data from ASCEND.[34,35] The results of the MAIC for both studies is shown in Table 4.27. Results were also validated by company's clinical experts, who suggested they were clinically plausible.[6] The company justified the CMA approach based on the assumption of non-inferiority.[6]

Table 4.27: Summary of MAIC results for zanubrutinib versus acalabrutinib for patients with R/R CLL- ELEVATE-RR

	PFS (IRC) hazard ratio (95% CI)	OS hazard ratio (95% CI)
MAIC using ELEVATE-RR		
Model 1	[redacted]	[redacted]

Model 2	[redacted]	[redacted]
MAIC using ASCEND		
Model 1	[redacted]	[redacted]
Model 2	[redacted]	[redacted]

Source: CS, Table 106[6]
Abbreviations: Cl = Confidence interval; CLL = Chronic lymphocytic leukaemia; CS = Company submission; MAIC = Matching-adjusted indirect comparison; OS = Overall survival; PFS = Progression-free survival; R/R = Relapsed or refractory.

EAG comment: As mentioned previously (see Sections 1.4, 1.5, 3.3.2.5 and 3.4), the EAG has concerns with the company's assumption of non-inferiority between zanubrutinib and acalabrutinib in R/R CLL. The EAG considers that the company has not provided sufficient evidence of non-inferiority, due to the wide 95% CIs which include clinically meaningful differences. A more appropriate interpretation of the MAIC results is that they provide no evidence of a difference in effectiveness. Therefore, the EAG considers that a CUA would have been more appropriate in this comparison than the CMA approach the company adopted. The EAG acknowledges the adoption of a CUA as the company's base-case may not have changed the conclusions, as illustrated by the CUAs undertaken by both the company, in scenario analyses (see Section 5.2.1.2) and the EAG in their base-case analysis (see Section 6.3.1). However, the EAG cannot be certain of these conclusions due to limitations with the modelling associated with applying a CUA to this economic model (see Section 4.4.2.1).

4.4.6.2.2 Zanubrutinib versus ibrutinib

Evidence from the ALPINE trial suggests that zanubrutinib is clinically superior to ibrutinib based on study results showing statistically significant improvements in ORR from the INV-assessed data.[30] When compared with ibrutinib, zanubrutinib was associated with a statistically significant reduction in the risk of INV-assessed disease progression or death ([redacted]; p=0.0004 at the 01 December 2021 data cut-off).[88] Late breaking data from the 08 August 2022 data cut-off on PFS showed a statistically significant [redacted]reduction in both INV-assessed and IRC-assessed progression or death when compared to ibrutinib ([redacted].

Despite the ALPINE trial data suggesting comparatively better clinical outcomes for zanubrutinib relative to ibrutinib in patients with R/R CLL, the company assumed that zanubrutinib was clinically equivalent to ibrutinib and thus kept a CMA approach to model cost-effectiveness of zanubrutinib across all comparators.

EAG comment: The EAG agrees with the company that the CMA assumption, which imposes the assumption that the relative effectiveness of zanubrutinib versus ibrutinib is equivalent for OS and PFS outcomes, is potentially a conservative scenario for the economic model. As an alternative, the approach proposed by the EAG as a more appropriate representation of the decision problem is a CUA (see Section 6.3.1).

The EAG considers the assumption that zanubrutinib is non-inferior when compared with ibrutinib to be a conservative assumption given the results of the ALPINE trial (zanubrutinib was superior to ibrutinib for all clinical outcomes except OS). Clinical advice to the EAG suggested that they did not expect a statistically significant difference in OS, given the patient population. Therefore, the EAG is happy with the company's justification of a CMA approach in this comparison only.

4.4.7 Adverse events

The company used the same assumptions in assigning AEs for the R/R economic model as the untreated economic model (see Section 4.3.7). The only difference was that included AEs had to occur in ≥ 2% of patients. The AE profile of zanubrutinib and ibrutinib were taken from the ALPINE trial.[38] The AE profile of acalabrutinib was taken from the ASCEND trial.[35] A summary of grade 3 ≥ AEs by each treatment is presented in Table 4.28.

Table 4.28: Grade ≥ 3 treatment-related AEs occurring in ≥ 2% of patients by treatment

Treatment	Zanubrutinib	Ibrutinib	Acalabrutinib
Anaemia	2.47%	2.47%	11.69%
Thrombocytopenia	2.78%	3.09%	3.90%
Pneumonia	4.01%	7.41%	5.19%
Neutropenia	14.20%	13.89%	15.58%
Hypertension	13.27%	12.96%	1.95%
Neutrophil count decreased	4.32%	4.01%	1.30%
Source	ALPINE CSR[38]		ASCEND Ghia 2020[90]

Source: CS, Table 109[6]
Abbreviations: AE = Adverse event; CS = Company submission; CSR = Clinical study report.

The impact of AEs on HRQoL was only explored in the economic model in a scenario analysis. The company used the same assumption as in Section 4.3.7 and only assigned utility decrements associated with AEs in the first cycle of the model. Utility decrements associated with AEs were not collected as part of the ALPINE study. Therefore, utility decrements were sourced from previous NICE appraisals in CLL and the published literature. No scenario analyses were conducted in relation to the AE disutilities. Disutility values for the AEs include in the economic model are presented in Table 4.29.

Table 4.29: Utility decrements and duration estimates by AE

AE	Disutility	Source	Duration (days)	Source
Anaemia	–0.090	TA487[69]	23.21	TA487[69]
Thrombocytopenia	–0.110	TA487[69]	23.21	TA487[69]
Pneumonia	–0.195	Tolley 2013[70]	18.20	TA359[71]
Neutropenia	–0.163	TA487[69]	15.09	TA487[69]
Hypertension	–0.020	Wehler 2018[72]	21.00	Assumption
Neutrophil count decreased	–0.163	TA487[69]	15.09	TA487[69]

Source: CS, Table 110[6]
Abbreviations: AE = Adverse event; CS = Company submission; TA = Technology appraisal.

EAG comment: Please see Section 4.3.7 as the EAG has the same concerns regarding the source and application of AEs in the R/R CLL economic model.

4.4.8 Health-related quality of life

4.4.8.1 Health-related quality of life data identified in the review

Please see Section 4.3.8.1 for a review of the HRQoL data identified in the SLR.

4.4.8.2 Health state utility values

A CUA was undertaken by the company as a scenario analysis only. The CS provided HRQoL data collected from the ALPINE trial.[88] Utility data were collected using the EQ-5D-5L administered at baseline and then every 12 weeks from the start of cycle 1 until disease progression, then every 24 weeks in the long-term follow-up after disease progression.

The CS stated that utility values were generated by mapping the EQ-5D-5L data to the EQ-5D-3L using a cross-walk algorithm and analysed using mixed-effect linear regression with a random intercept and adjusted for baseline utility (mean value of eligible population).[6,19,79] The CS states that the potential effect of treatment progression status on utility was explored both individually and jointly in the same model.[6] Utility values for the economic model were estimated by pooling data across the treatment arms in ALPINE, as there was no evidence of systematic differences in HRQoL across study arms.[6]

EAG comment: The CS only presented information on EQ-5D-5L utility scores graphically, so the EAG requested the company to provide descriptive summaries (mean and measure of variance) of the EQ-5D-5L utility data for each time point data were collected. The company provided this data from the ALPINE trial for two data cut-off time points, details of which are in Tables 4.30 and 4.31.

Table 4.30: Descriptive summaries of EQ-5D-5L for ALPINE (DCO 31 December 2020)

Assessment	Zanubrutinib (N=280)		Ibrutinib (N=271)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to clarification letter[12]
Abbreviations: CI = Confidence interval; DCO = Data cut-off; NE = Not evaluated; SD = Standard deviation.

Table 4.31: Descriptive summaries of EQ-5D-5L for ALPINE (DCO 01 December 2021)

Assessment	Zanubrutinib (N=309)		Ibrutinib (N=300)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]

Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 31 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 34 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 37 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 8	[redacted]	[redacted]	[redacted]	[redacted]
Long-term follow-up 10	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to clarification letter[12]
Abbreviations: CI = Confidence interval; DCO = Data cut-off; NE = Not evaluated; SD = Standard deviation.

The predicted utility for the health states included in the model (PF and PD) in comparison to utilities based on published general population values (see Table 4.32). The CS states that progression was INV-assessed to align with the PFS endpoint used in the base-case survival analysis.[6] Given the data for PF and PD were higher than the UK general population data, the CS states that the data from the ALPINE trial lacked face validity.[6] Therefore, data from the ALPINE trial were not used in the cost-utility scenario analysis.

Table 4.32: Utility Model Including Progression Status as Predictors

Predictor	No. of Patients	No. of Obs.	Coefficient (95% CI)	Source
Predicted utility for health states				
PF	[redacted]	[redacted]	[redacted]	ALPINE[88]
PD	[redacted]	[redacted]	[redacted]	
Mean utility based on published general population in UK				
General population irrespective of health status (65 to ≤ 70)			0.804 (0.790, 0.817)	Ara and Brazier 2011;[81] supplementary Table A4
General population with health condition "cancer" (65 to ≤ 70)			0.730 (0.652, 0.807)	
General population without health condition "cancer" (65 to ≤ 70)			0.808 (0.794, 0.821)	

Source: CS, Table 108[6]
Abbreviations: CI = Confidence interval; PD = Progressed disease; PF = Progression-free.

For the cost-utility scenario analysis, the company used published utility values to inform the PF and PD health states.[3] The PF utility was 0.748; no justification was provided as to why this differed from the untreated CLL model.[6] The company assumed the same utility value for PD (0.6) that was used in the untreated model.[6] Table 4.33 presents a summary of the values used in the cost-utility scenario analysis.

Table 4.33: Summary of utility vlaues for the cost-utility analysis

State	Utility value: mean (standard error)	95% CI	Source
PF	0.748 (0.0740)	0.589, 0.879	Utilities reported in TA516*, generated using EQ-5D estimates from Study 116[3]
PD	0.600 (0.0597)	0.481, 0.714	Holzner et al. 2004[82]

Source: CS, Table 111[6]
Abbreviations: CI = Confidence interval; PD = Progressed disease; PF = Progression-free; TA = Technology appraisal.
*The above source text for PF has a typo, it should be TA561, not TA516.

EAG comment: The EAG comments in Section 4.3.8.2 also apply to the assumptions made by the company for the R/R CLL economic model. In addition, there was an error in the referencing for PF utility values. The CS states this is TA516, while the EAG believes this to be TA561.[3] Overall, the EAG considers the health state utility values used in the economic model to be associated with a high degree of uncertainty.

4.4.9 Resources and costs

4.4.9.1 Resource use and costs data identified in the review

Please see Section 4.3.9.1 for a review of the resource use and cost data identified in the SLR.

4.4.9.2 Intervention and comparator drug costs

Drug costs for the R/R CLL model were assumed to be the same as those in the untreated CLL model (see Section 4.3.9.2).

4.4.9.2.1 Dose, vial sharing and dose intensity

The same dosing information for the untreated CLL model was assumed for the R/R CLL model (see Section 4.3.9.2.1).

EAG comment: The EAG has no further comment on acquisition costs beyond what was already discussed in Section 4.3.9.2.1.

4.4.9.2.2 Acquisition costs

In the base-case analysis, BTKi treatment was given until disease progression; scenario analyses explored other treatment duration assumptions.

It was assumed by the company, based on 2022 BSH guidelines, that the majority of patients received BCL2i treatment (VenR) following disease progression and a small proportion of these patients would

receive treatment with idelalisib-rituximab.[6] Based on clinical, health economic and statistical advice the company assumed that 80% of patients, following disease progression, would receive VenR and 20% would receive idelalisib-rituximab.[6] Drug package price and cost per cycle for first line treatments were presented previously in Table 4.17. Acquisition costs for second-line treatments in the R/R CLL population are presented in Table 4.34.

Table 4.34: Subsequent treatments drug package price and total acquisition cost

Treatment	Dosage strength	Pack size/vial volume	Admin route	Cost per pack (£)	Mean duration of treatment (cycles)	Total acquisition cost (£)
Idelalisib	150mg	60mg	Oral	3,311.80	20.3	71,359.86
Rituximab	10mg/ml 10mg/ml	10ml 50ml	IV	157.17 785.84	8	
Venetoclax	100mg	7 mg	Oral	299.34	26	130,008.37
Rituximab	10mg/ml 10mg/ml	10ml 50ml	IV	157.17 785.84	6	

Source: CS, Table 114[6]
Abbreviations: CS = Company submission; IV = Intravenous; mg = Milligram; ml = Millilitre.

EAG comment: The clinical expert consulted by the EAG suggested that treatment with idelalisib is very rare in the UK; a proportion of 5% of patients receiving idelalisib combination is presented in the scenario analysis by the EAG (see Section 6.3.2). The EAG has no further comment on acquisition costs beyond what was already discussed in Section 4.3.9.2.2.

4.4.9.2.3 Administration costs

Drug administration costs were only applied to CIT drugs (idelalisib and rituximab) and are presented in Table 4.35.[6]

Table 4.35: Drug administration costs

Description of cost	Use in model	Unit cost (£)	Source
Delivered oral chemotherapy	Idelalisib: one administration within Cycle 1	54.00	National Schedule of NHS Costs 2020/21[86]
Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance	Rituximab: one administration within Cycle 1	526.52	
Deliver Subsequent Elements of a Chemotherapy Cycle	Rituximab: one administration per cycle for Cycles 2-6 or Cycles 2-8	470.62	

Source: CS, Table 115[6]
Abbreviations: CS = Company submission; NHS = National Health Service.

EAG comment: The EAG have no concerns in how drug administration costs were estimated.

4.4.9.3 Monitoring and disease management costs

Costs for TLS management included in the model are as reported in Section **Error! Reference source not found.** of the EAG report.

EAG comment: The EAG has no further comment on acquisition costs beyond what was already discussed in Section 4.3.9.3.

4.4.9.4 Adverse effects costs

As previously discussed in Section 4.4.7, all grade ≥ 3 treatment-related AEs occurring in ≥ 2% of participants receiving BTKi treatment in were included in the company model. Total AE costs were calculated based on the proportion of AE incidences for each of the BTKi treatments (see Table 4.28) and the unit costs in Table 4.36.

Table 4.36: AE management costs

Adverse event	Cost (£)	Source	Comment
Anaemia	721.99	National Schedule of NHS Costs 2020/21[86]	SA09 Other Red Blood Cell Disorders with CC Score 0-5, non-elective short stay
Hypertension	537.86	National Schedule of NHS Costs 2020/21[86]	EB04Z Hypertension, non-elective short stay
Neutropenia	761.01	National Schedule of NHS Costs 2020/21[86]	SA35 Agranulocytosis, non-elective short stay
Neutrophil count decreased	761.01	National Schedule of NHS Costs 2020/21[86]	SA35 Agranulocytosis, non-elective short stay
Pneumonia	782.27	National Schedule of NHS Costs 2020/21[86]	DZ11 Lobar, Atypical or Viral Pneumonia, non-elective short stay
Thrombocytopenia	881.88	National Schedule of NHS Costs 2020/21[86]	SA12 Thrombocytopenia, non-elective short stay
Source: CS, Table 116[6] Abbreviations: AE = Adverse event; CC = Complication and comorbidity; NHS = National Health Service.			

EAG comment: The EAG does not have any concerns about the unit costs used by the company. However, the same concerns raised about the inclusion and duration of AEs raised in Section 4.3.7 apply here.

4.4.9.5 Health state costs

Costs related to routine follow-up and disease management included in the R/R CLL economic model were the same as those reported for the untreated CLL economic model (see Section 4.3.9.5).

EAG comment: The EAG has no further comment on acquisition costs beyond what was already discussed in Section 4.3.9.5.

4.4.9.6 Terminal care costs

Costs associated with terminal care included in the R/R CLL economic model were the same as those reported for the untreated CLL economic model (see Section 4.3.9.6).

EAG comment: The EAG has no further comment on acquisition costs beyond what was already discussed in Section 4.3.9.6

4.4.10 Summary of company assumptions applied in base-case analysis

The company analyses the cost-effectiveness of zanubrutinib versus ibrutinib or acalabrutinib using a CMA approach, assuming equivalent effectiveness in terms of survival and quality of life across treatment and comparator arms. The justification of the CMA approach was founded on the results obtained from the MAIC analyses comparing data from ALPINE[88] with either ELEVATE-RR[36] or ASCEND[35], to demonstrate non-inferiority of zanubrutinib versus acalabrutinib on key survival outcomes.

The EAG considers that the MAIC analyses do not present sufficient evidence of non-inferiority, and instead present no evidence of a difference due to limited data and estimate imprecision. Henceforth, the EAG does not consider a CMA to be the best approach to represent the decision problem the decision problem in the comparison of zanubrutinib with acalabrutinib. The EAG acknowledges the adoption of a CUA as the company's base-case may not have changed the conclusions, as illustrated by the CUAs undertaken by both the company, in scenario analyses (see Section 5.2.1.2) and the EAG in their base-case analysis (see Section 6.3.1). However, the EAG cannot be certain of these conclusions due to limitations with the modelling associated with applying a CUA to this economic model (see Section 4.4.2.1).

Table 4.37 summaries the assumptions made by the company in their base-case economic model in R/R CLL.

Table 4.37: Summary of assumptions applied in the base-case analysis for R/R CLL

Parameter	Details	Section	Source
Population	R/R CLL with at least one previous therapy	Section 4.4.3	ALPINE trial[30]
Perspective	Payer (NHS England and PSS)	Section 4.4.5	Assumption
Time horizon	Lifetime (30 years)	Section 4.4.5	Assumption
Proportion females	[redacted]	Section 4.4.3	ALPINE trial[30]
Starting age	[redacted] years	Section 4.4.3	ALPINE trial[30]
BSA	1.92 m^2	Section 4.4.3	ALPINE trial[30]
Half-cycle correction	Yes	Section 4.4.2	Assumption
Discount rate	0.035	Section 4.4.5	NICE guidelines[19]
Survival models			
PFS distribution	Weibull	Section 4.4.6.1.1	Based on ALPINE trial data[30]
OS distribution	Weibull	Section 4.4.6.1.2	Based on ALPINE trial data[30]
Hazard ratios			
PFS zanubrutinib vs acalabrutinib	1	Section 4.4.6.2	CMA assumption
PFS zanubrutinib vs acalabrutinib	1		

OS zanubrutinib vs acalabrutinib	1		
OS zanubrutinib vs acalabrutinib	1		
AE incidence			
Zanubrutinib	Grade ≥ 3 occurring in > 2% of patients	Section 4.4.7	ALPINE trial[30]
Acalabrutinib			ASCEND trial[35]
Ibrutinib			ALPINE trial[30]
Utility values			
PF	0.748	Section 4.4.8	NICE TA561[3]
PD	0.6		Holzner et al, 2004[82]
Costs and resource use			
Resource use	Resource use values from the literature	Section 4.4.8	NICE TA 689[64]
End of life costs	Resource use and costs from the literature		Round 2015[87]
TSL management costs	One-time monitoring for venetoclax		Seymour *et al*., 2018[9] and NICE TA561[3]
Treatment acquisition	PAS discount applied to zanubrutinib		BNF,[63] company data
Treatment duration	Until progression or death	Section 4.4.4	Assumption
Subsequent treatment	80% receive VenR; 20% receive idelalisib rituximab	Section 4.4.8	BSH guidelines,[2] Assumption

Source: Created by the EAG based on CS, Table 89[6]
Abbreviations: AE = Adverse event; BNF = British National Formulary; BSA = Body surface area; BSH = British Society for Haematology; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = Progressed disease; PF = Progression-free; PFS = Progression-free survival; PSS = Personal Social Services; R/R = Relapsed or refractory; TSL = Tumour lysis syndrome prophylaxis; VenR = Venetoclax-rituximab.

5 COST-EFFECTIVENESS RESULTS

The company's cost-effectiveness results which include the confidential patient access scheme (PAS) price for zanubrutinib, are presented for the untreated CLL population in Section 5.1 and for the R/R population in Section 5.2.

5.1 Company's cost-effectiveness results for the previously untreated population

In the previously untreated CLL ("unfit" and "high-risk" populations) base-case economic model zanubrutinib was associated with cost savings of [redacted] compared with acalabrutinib and [redacted] compared with ibrutinib. Results from the deterministic one-way sensitivity analysis (OWSA) indicated that the analysis was most sensitive to survival coefficients for the generalised gamma TTP curve.[6]

The base-case deterministic and probabilistic results for the pooled SEQUOIA arm A and arm C population are presented in Table 5.1.

Table 5.1: Base-case results for the previously untreated CLL population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs savings (£) for zanubrutinib
Deterministic				
Zanubrutinib	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic				
Zanubrutinib	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Tables 91 and 92[6]
Abbreviations: CS = Company submission; LYG = Life years gained; QALYs = Quality-adjusted life years.

EAG comment: As presented in the CS, the company base-case analysis shows that treatment with zanubrutinib is associated with cost savings compared with acalabrutinib or ibrutinib. This finding was consistent across all scenario analyses conducted.[6] However, the EAG have previously questioned the appropriateness of a CMA given that the MAIC results did not provide sufficient evidence of non-inferiority from zanubrutinib compared with acalabrutinib in untreated CLL (see Sections 3.3 and 3.4). The EAG considers a CUA approach, which the company adopted in scenario analyses (see Section 4.3.2.1 and Table 5.2), to be more appropriate than the CMA approach used by the company in their basecase analysis as the best representation of the decision problem (see Section 4.3.6.2).

Also, the EAG have concerns with the effectiveness of zanubrutinib compared with ibrutinib in untreated CLL, given these data were based on the ALPINE trial which is in a R/R CLL population and a naïve comparison (see Section 4.3.4 and Section 4.3.6.2.3). The EAG is unsure that the company have sufficient data to support the comparison of zanubrutinib with ibrutinib in the combined "unfit" and "high-risk" untreated CLL populations given that the effectiveness of zanubrutinib compared with ibrutinib was estimated using the assumption that R/R is a suitable proxy for untreated "high-risk". Also, as ibrutinib would only be given as a treatment to untreated "high-risk" CLL patients the EAG is unsure on the usefulness of this comparison to the decision problem.

5.1.1 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) and scenario analyses.

5.1.1.1 Probabilistic sensitivity analysis

A PSA (n=1,000) was conducted to assess the impact of parameter uncertainty on the results of the base-case model and the results were recorded as total costs, outcomes; and incremental costs and outcomes.[6]. The results are presented in Table 5.1 and the cost and QALY plot is presented in Figure 5.1.

In the probabilistic analysis, treatment with zanubrutinib in patients with previously untreated CLL was associated with cost savings of and [redacted] compared with ibrutinib and acalabrutinib, respectively. The CS states that the probabilistic results are close to the deterministic results and the model is robust to parameter uncertainty.[6] Furthermore, the probabilistic analysis indicated that zanubrutinib had a [redacted] probability of being considered cost-effective at a £20,000 per QALY threshold, and a [redacted] probability at the £30,000 threshold. Similarly, zanubrutinib versus ibrutinib had a [redacted] probability of being considered cost-effective at the £20,000 per QALY threshold, and a [redacted] probability at the £30,000 threshold.

Figure 5.1: Total cost and QALY scatterplot for zanubrutinib versus ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Source: CS, Figure 54[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; CS = Company submission; QALY = Quality-adjusted life year.

EAG comment: Figure 5.1 illustrates the uncertainty in costs between the zanubrutinib when compared with acalabrutinib and ibrutinib. For all of the iterations shown, zanubrutinib is always less costly than its comparators. The cost-effectiveness plane also illustrates uncertainty in QALYs. However, it should be noted that there are no observable differences in QALYs between the interventions as the CMA assumed that clinical effectiveness and hence QALYs were equivalent between the treatments.

5.1.1.2 Scenario analysis

The company undertook several scenario analyses to estimate the impact of certain model inputs and assumptions on the cost-effectiveness results (CS, Table 95).[6] Deterministic scenario analysis results for zanubrutinib compared with both ibrutinib and acalabrutinib are presented in Table 5.2. The list of parameters or assumptions changed in scenario analysis include the following:

- Discount rate
- TTP endpoint (INV-assessed)
- TTP/PrePS curve for zanubrutinib
- Use TTTD data for zanubrutinib
- PPS curve for BTKi2L PFS curve for BTKi
- Exclude wastage
- Exclude AE costs
- Apply AE impact to QALYs
- Unfit/high risk data within the CMA framework
- CUA using pooled data from SEQUOIA Arm A and Arm C, applying HRs derived from ELEVATE-TN MAIC (Model 1 and Model 2), Mato *et al*., (2018)[5] comparison and R/R data as a proxy.
- CUAs using Arm A and Arm C data separately applying HRs derived from ELEVATE-TN MAIC (Model 1 and Model 2), Mato *et al*., (2018)[5] comparison and R/R data as a proxy.

The results of the deterministic scenario analyses undertaken by the company had variable impacts on the incremental costs for the two pairwise comparisons.

- Using unfit data (SEQUOIA arm A) showed a moderate change in incremental costs, while using the high-risk data (SEQUOIA arm C) resulted in larger cost-savings compared to the base-case results, with a cost saving of [redacted] for zanubrutinib versus ibrutinib and [redacted] for zanubrutinib versus acalabrutinib.
- The largest difference compared to the company base-case results was when the discount rate was changed. Assuming a 0% discount rate resulted in an incremental cost of [redacted] and[redacted] for zanubrutinib versus ibrutinib and zanubrutinib versus acalabrutinib respectively. Assuming a higher discount rate (6%) resulted in an incremental cost of [redacted] cost saving for zanubrutinib versus ibrutinib and [redacted] for zanubrutinib versus acalabrutinib.
- Log-normal and exponential distribution for TTP/PrePS curves for zanubrutinib resulted in a moderate change in incremental costs for both comparators. Using a log-normal distribution resulted in an incremental cost of [redacted] for zanubrutinib versus ibrutinib and [redacted] for zanubrutinib versus acalabrutinib. Applying an exponential distribution resulted in an incremental cost of [redacted] for zanubrutinib versus ibrutinib and [redacted] for zanubrutinib versus acalabrutinib.

Table 5.2: Summary of scenario analyses results for zanubrutinib versus ibrutinib and acalabrutinib – deterministic

Scenario	zanubrutinib vs ibrutinib				zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base-case	[redacted]				[redacted]			
No Discounting	[redacted]				[redacted]			
High Discount rates (6%)	[redacted]				[redacted]			
TTP endpoint (INV)	[redacted]				[redacted]			
TTP/PrePS curve for zanubrutinib (Log-normal)	[redacted]				[redacted]			
TTP/PrePS curve for zanubrutinib (exponential)	[redacted]				[redacted]			
Use TTTD data for zanubrutinib	[redacted]				[redacted]			
PPS curve for BTKi (Weibull)	[redacted]				[redacted]			
2L PFS curve for BTKi (Generalised Gamma)	[redacted]				[redacted]			
2L PFS curve for BTKi (Weibull)	[redacted]				[redacted]			
Exclude wastage	[redacted]				[redacted]			
Exclude AE costs	[redacted]				[redacted]			
Apply AE impact to QALYs (cost-utility)	[redacted]		[redacted]	Dominant	[redacted]		[redacted]	Dominant
Unfit data (cost-min)	[redacted]				[redacted]			

High-risk data (cost-min)	[redacted]				[redacted]			
Pooled (cost-utility – ELEVATE-Untreated CLL MAIC model 1)					[redacted]	[redacted]	[redacted]	Dominant
Pooled (cost-utility – ELEVATE-Untreated CLL MAIC model 2)					[redacted]	[redacted]	[redacted]	Dominant
Unfit data (cost-utility – ELEVATE-Untreated CLL MAIC model 1)					[redacted]	[redacted]	[redacted]	Dominant
Unfit data (cost-utility – ELEVATE-Untreated CLL MAIC model 2)					[redacted]	[redacted]	[redacted]	Dominant
High-risk data (cost-utility – ELEVATE-Untreated CLL MAIC model 1)					[redacted]	[redacted]	[redacted]	Dominant
High-risk data (cost-utility – ELEVATE-Untreated CLL MAIC model 2)					[redacted]	[redacted]	[redacted]	Dominant
High-risk data (cost-utility – R/R as proxy)	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
High-risk data (cost-utility – naïve	[redacted]	[redacted]	[redacted]	Dominant	[redacted]			

comparison based on Mato *et al*., 2018)								

Source: CS, Table 95[6]
Abbreviations: AE = Adverse event; BTKi = Bruton tyrosine kinase inhibitor; CLL = Chronic lymphocytic leukaemia; CS = Company submission; ICER = Incremental cost-effectiveness ratio; INV = Investigator; LYG= Life years gained; MAIC = Matching-adjusted indirect comparison; PFS = Progression-free survival; PPS = Post-progression survival; QALY= Quality-adjusted life year; R/R = Relapsed or refractory; TTTD = Time to discontinuation; TTP = Time-to-progression.

EAG Comment: Overall, the EAG is satisfied with the exploration of uncertainty in model parameters undertaken by the company. However, there are few points EAG would like to raise:

- With respect to the mean starting age (years) of the patients in the model and their reasonable life expectancy, the EAG would have liked to seen scenario analyses exploring the effect on costs (and, given the EAGs concerns over the adoption of CMA, cost-effectiveness) of reducing the time horizon to 10 years and 15 years.
- In practice, progression of disease may only be clinically confirmed at a regular follow-up point (at the end or start of the cycle) and, hence, the costs associated with the disease progression would only be incurred at the end or start of a cycle. The costs of drugs prescribed in each cycle occurred in full at the point they were prescribed and irrespective of when a person died within the model cycle. Therefore, it would be useful to see how the results changed when half-cycle correction was not considered.
- Exclusion of wastage is one of the scenarios modelled.[6] The CS mentions that the wastage for IV drugs was taken into consideration.[6] However, the report does not provide any information on the wastage and its associated costs used in the model. Furthermore, in the case of oral drugs, patients who die without completing their full course of oral treatment will inevitably accrue some wastage.
- The CS states that the relative dosing intensity (RDI) is assumed to be 100% for all treatments and refers to TA689 to support this assumption.[6,64] However, the EAG consider this to be an optimistic assumption that can potentially overestimate acquisition costs across the intervention arms (see Section 4.3.9.2.2).

5.1.1.3 Deterministic sensitivity analysis

DSAs were performed to explore the effect of uncertainty associated with varying individual model inputs or with varying groups of individual model inputs on incremental costs. The results of the DSAs are summarised in Table 5.3 and Figure 5.2 for ibrutinib and Table 5.4 and Figure 5.3 for acalabrutinib. The most influential factors on the DSA were the survival coefficients for the generalised gamma TTP curve in both the comparisons with ibrutinib and acalabrutinib.[6]

Table 5.3: DSA results (incremental costs) for zanubrutinib versus ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Generalised Gamma model to project TTP for zanubrutinib		
Shape for Generalised Gamma model to project TTP for zanubrutinib		
Starting age		
Shape for Generalised Gamma model to project pre-progression survival for All treatments		
Proportion female		
Scale for Generalised Gamma zanubrutinib		

Cost of AEs per cycle with ibrutinib	[redacted]	[redacted]
Intercept for Generalised Gamma model to project pre-progression survival for All treatments	[redacted]	[redacted]
Cost of AEs per cycle with zanubrutinib	[redacted]	[redacted]

Source: CS, Table 93[6]
Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; TPP = Time-to-progression.

Figure 5.2: Tornado plot of DSA results (incremental costs) for zanubrutinib versus ibrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Source: Company response to clarification letter, Figure 2[12]
Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; TPP = Time-to-progression.

Table 5.4: DSA results (incremental costs) for zanubrutinib versus acalabrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Generalised Gamma model to project TTP for zanubrutinib	[redacted]	[redacted]
Shape for Generalised Gamma model to project TTP for zanubrutinib	[redacted]	[redacted]
Starting age	[redacted]	[redacted]
Shape for Generalised Gamma model to project pre-progression survival for all treatments	[redacted]	[redacted]
Proportion female	[redacted]	[redacted]
Scale for Generalised Gamma model to project TTP for zanubrutinib	[redacted]	[redacted]
Intercept for Generalised Gamma model to project pre-progression survival for all treatments	[redacted]	[redacted]
Cost of AEs per cycle with acalabrutinib	[redacted]	[redacted]
Cost of AEs per cycle with zanubrutinib	[redacted]	[redacted]

Source: CS, Table 94[6]
Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; TTP = Time-to-progression.

Figure 5.3: Tornado plot of DSA results (incremental costs) for zanubrutinib versus acalabrutinib in patients with previously untreated CLL (pooled SEQUOIA arm A and arm C)

Source: Company response to clarification letter, Figure 3[12]
Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; TPP = Time-to-progression.

EAG comment: The EAG is satisfied with the DSA and the presentation of results.

5.1.2 Subgroup analysis

The company used pooled data from SEQUOIA arm A and arm C in base-case, which reflects the full cohort of "unfit" and "high-risk" previously untreated patients with CLL. Scenario analyses were also undertaken using data from SEQUOIA arm A, the "unfit" population, and arm C, the "high-risk" population, with details of the extrapolations and curve selection presented in Appendix M.[65]

In a comparison with acalabrutinib using data from SEQUOIA arm A to mirror the "unfit" population, zanubrutinib was associated with a cost saving of £[redacted]. In a further scenario analysis using a cost-utility approach in the "unfit" population, zanubrutinib associated with a cost saving of [redacted] and was more effective ([redacted] QALY gain) and so dominated acalabrutinib.[6]

In a comparison with acalabrutinib and ibrutinib using data from SEQUOIA arm C to mirror the "high-risk" population, zanubrutinib was associated with a cost saving of £[redacted] compared to acalabrutinib and £[redacted] compared to ibrutinib. In a further scenario analysis using a cost-utility approach in the "high-risk" population, zanubrutinib dominated both acalabrutinib (£[redacted] cost saving; [redacted] QALY gain) and ibrutinib (£[redacted] cost saving; [redacted] QALY gain). In a scenario analysis using the results from the naïve comparison (CS Section B.3a.3.4.2 and EAG report Section 4.3.6.2.3) versus ibrutinib using Mato *et al*., (2018) data,[5] zanubrutinib also dominated ibrutinib (there was a £[redacted] cost saving and [redacted] QALY gain).[6]

EAG Comment: As mentioned in the CS,[6]and shown in Appendix M,[65] zanubrutinib was found to be cost-effective in most scenario analyses. Although zanubrutinib was reported to result in large cost saving in all scenarios, using data from SEQUOIA arm A to mirror the "unfit" population is the least cost saving scenario among all those scenarios presented, a critique to this approach was presented in in Section 4.2.6.2.1.

5.1.3 Benefits not captured in the QALY calculation

In the CS, the company state that zanubrutinib is likely to reduce the risk of AEs compared with ibrutinib and acalabrutinib, particularly for cardiac AEs and tolerability issues.[6] However, as the company's base-case analysis was a CMA these potential benefits were not captured. Based on the results of another trial, over the short-term (median follow-up 12 months) zanubrutinib has shown safety and tolerability advantages compared to other BTKis.[91]

EAG Comment: The EAG agree that there could be additional benefits (or harms) associated with zanubrutinib based on the evidence provided in the CS and suggest that this finding provides further justification that the company should have adopted a cost-utility approach for their base-case analysis. It also supports the EAG comments (see Section 4.3.7) in that AEs should have been incorporated into the economic model for more than one cycle.

5.1.4 Severity of the condition

The company did not include a severity analysis in the CS.

5.1.5 Model validation

5.1.5.1 Face validity assessment and technical verification

A third-party health economist employed by the company carried out a review of the face validity of the model and conducted a verification of model calculations and data sources. This process also

included extreme-value sensitivity analysis and logic tests.[6] Additionally, expert opinion was obtained from clinicians and economists (in the advisory board organised by the company) to validate the model inputs and outputs.[6] In particular, the advisory board was used to validate the survival extrapolations, choice of comparators and assumption of non-inferiority between zanubrutinib and acalabrutinib and ibrutinib, respectively.[6] Key model assumptions, inputs and outputs were also validated against previous NICE TAs and published literature reviewing treatments for CLL. The CS reports that feedback from the validation was addressed and the model was refined post validation.[6]

EAG comment: Overall, the EAG was satisfied with the steps taken for face validation and technical verification.

5.1.5.2 Comparison with external data

Long-term published data (from ELEVATE-TN and RESONATE-2 trials[29,33]) in patients with previously untreated CLL were used to validate the modelled survival outputs. The company state that, as shown in Table 5.5, the close alignment of PFS and OS for the three BTKis to the clinical trial data increased the validity of the company results.[6]

Table 5.5: Comparison of modelled PFS and OS versus published clinical trial data in previously untreated CLL

Dataset	Proportion of patients at 1 year	Proportion of patients at 5 years	Proportion of patients at 8 years
PFS			
Modelled BTKis	93%	68%	56%
RESONATE-2 ibrutinib arm	94%	67%	60%
ELEVATE-TN acalabrutinib arm	96%	NR	NR
OS*			
Modelled BTKis	97%	87%	79%
RESONATE-2 ibrutinib arm	97%	83%	NR

Source: CS, Table 98[6]
*Long-term OS not available from ELEVATE-TN.
Abbreviations: BTKi = Bruton tyrosine kinase inhibitor; CLL = Chronic lymphocytic leukaemia; NR = Not reached; OS = Overall survival; PFS = Progression-free survival.

EAG comment: As stated in Section 4.3.6.1, the EAG have concerns about the appropriateness of the comparisons presented given the population characteristics in some of these studies.

5.2 Company's cost-effectiveness results for the R/R population

In the base-case deterministic CMA, over a lifetime horizon treatment with zanubrutinib in R/R CLL was associated with cost-savings of [redacted] and [redacted] per person, compared with ibrutinib and acalabrutinib, respectively. The results of the CS base-case are presented in Table 5.6.

Table 5.6: Base-case results in patients with R/R CLL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)
Deterministic				
Zanubrutinib	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic				
Zanubrutinib	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

Source: CA, Tables 120 and 121[6]
Abbreviations: LYG = Life years gained; QALYs = Quality-adjusted life years; R/R = Relapsed or Refractory.

EAG comment: As presented in the CS, the company base-case analysis shows that treatment with zanubrutinib is associated with cost savings when compared with acalabrutinib and ibrutinib and across all scenario analyses conducted, zanubrutinib remained cost saving compared with acalabrutinib and ibrutinib.[6] However, the EAG have previously questioned the appropriateness of a CMA given that the MAIC results did not provide sufficient evidence of non-inferiority from zanubrutinib compared with acalabrutinib in R/R CLL (see Sections 3.3 and 3.4). Therefore, the EAG considers a CUA approach, which was adopted by the company in scenario analyses, to be more appropriate than the CMA approach used by the company in their base-case analysis as the best representation of the decision problem (see Section 4.4.6.2). However, the EAG acknowledge the adoption of a CMA to compare zanubrutinib with ibrutinib in R/R CLL is a conservative assumption.

5.2.1 Company's sensitivity analysis

The company undertook DSA, PSA as well as scenario analyses to explore uncertainty in the results.

5.2.1.1 Probabilistic sensitivity analysis

A PSA (n=1,000) was conducted to assess the impact of parameter uncertainty on the results of the base-case model and the results were recorded as total costs, outcomes; and incremental costs and outcomes. The results were presented in tables (Table 5.6) and scatterplot (Figure 5.4).

For the probabilistic analysis, treatment with zanubrutinib in patients with R/R CLL amount to cost-savings of [redacted] and [redacted] for ibrutinib and acalabrutinib, respectively. The CS states that the probabilistic results lie close to the deterministic results and the model is robust to parameter uncertainty.[6]

Figure 5.4: Total cost and QALY scatterplot for zanubrutinib versus ibrutinib and acalabrutinib in patients with R/R CLL

Source: CS, Figure 62[6]
Abbreviations: CLL = Chronic lymphocytic leukaemia; QALY = Quality-adjusted life year; R/R = Relapsed or refractory.

EAG comment: The deterministic and probabilistic results lie close to each other and the company's statement of robustness of the model in terms of parameter uncertainty appears reasonable.,

5.2.1.2 Scenario analysis

The company conducted several scenario analyses for both zanubrutinib compared with ibrutinib and acalabrutinib. The CS presents the results of both the deterministic and probabilistic analysis (1,000 iterations) for each scenario analysed (CS, Tables 5.7 and 5.8).[6] In the scenario analyses, the company also carried out a CUA using HRs generated from Model 1 and Model 2 of the MAIC with ELEVATE-RR (where zanubrutinib was the dominant treatment compared with acalabrutinib), and using HRs generated from Model 1 and Model 2 of the MAIC with ASCEND (where zanubrutinib was slightly less effective and less costly than acalabrutinib), as well as using data extrapolated from the ALPINE trial (where zanubrutinib was dominant over ibrutinib). The results showed cost savings ranging between [redacted] and [redacted] for zanubrutinib compared with ibrutinib and cost savings ranging between [redacted] and [redacted] for zanubrutinib compared with acalabrutinib. The probabilistic results for the scenarios analysed were close to the deterministic results.

The only substantially influential scenario for both comparators that increased the cost savings was when a 0% discount rate was adopted (with incremental costs [redacted] and [redacted] compared against ibrutinib and acalabrutinib respectively).

The list of parameters assumptions changed in the economic model include the following:

- Discount rate
- PFS endpoint (IRC-assessed)
- PFS parametric survival model
- OS parametric survival model
- Excluding wastage
- Excluding AE costs
- Using TTTD data for zanubrutinib and ibrutinib
- A CUA using parameters from the MAIC in ELEVATE RR for acalabrutinib
- A CUA using parameters from the MAIC in ASCEND for acalabrutinib
- Applying AE impact to QALYs
- A CUA using ibrutinib ALPINE extrapolation
- CUAs using parameters from the MAIC in ELEVATE RR for acalabrutinib (Model 1 and Model 2)
- CUAs using parameters from the MAIC in ASCEND (Model 1 and Model 2) for acalabrutinib
- CUA using Arm A and Arm C data separately applying HRs derived from ELEVATE-TN MAIC (Model 1 and Model 2), Mato et al. (2018) comparison and R/R data as a proxy.

The following scenarios reduced the cost savings observed in the company's base-case analysis:

- High discount rates (6%): cost savings of zanubrutinib versus ibrutinib ([redacted]) versus acalabrutinib ([redacted])
- 01 December 2020 data cut-off used for PFS and OS: cost savings of zanubrutinib versus ibrutinib ([redacted]); versus acalabrutinib ([redacted]).
- PFS endpoint (IRC): cost savings of zanubrutinib versus ibrutinib ([redacted]); versus acalabrutinib ([redacted]).
- PFS curve for zanubrutinib (Gompertz): cost savings of zanubrutinib versus ibrutinib ([redacted]); versus acalabrutinib ([redacted]).
- Use TTTD data for zanubrutinib and ibrutinib (zanubrutinib versus ibrutinib only): cost savings of zanubrutinib versus ibrutinib ([redacted]); versus ibrutinib ([redacted]).
- The CUA of zanubrutinib versus ibrutinib: incremental costs ([redacted]), incremental QALYs ([redacted])
- The CUA using MAIC 2 ASCEND results for acalabrutinib: incremental costs ([redacted]), incremental QALYs ([redacted])

Table 5.7: Summary of scenario analyses results for zanubrutinib versus ibrutinib and acalabrutinib – deterministic

Scenario	Zanubrutinib versus ibrutinib				Zanubrutinib versus acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER(£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base-case	[redacted]				[redacted]			
No Discounting	[redacted]				[redacted]			
High Discount rates (6%)	[redacted]				[redacted]			
December 2020 data cut for PFS and OS	[redacted]				[redacted]			
PFS endpoint (IRC)	[redacted]				[redacted]			
PFS curve for zanubrutinib (Gompertz)	[redacted]				[redacted]			
OS curve for zanubrutinib (Exponential)	[redacted]				[redacted]			
Exclude wastage	[redacted]				[redacted]			
Exclude AE costs	[redacted]				[redacted]			

Scenario	Zanubrutinib versus ibrutinib				Zanubrutinib versus acalabrutinib			
	Incremental costs (£)	**Incremental LYG**	**Incremental QALYs**	**ICER(£/QALY)**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY)**
Use TTTD data for zanubrutinib and ibrutinib	[redacted]				[redacted]			
Apply AE impact to QALYs	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
Cost-utility (Ibrutinib ALPINE extrapolation)	[redacted]	[redacted]	[redacted]	Dominant				
Cost-utility (acalabrutinib MAIC 1 ELEVATE-RR)					[redacted]	[redacted]	[redacted]	Dominant
Cost-utility (acalabrutinib MAIC 1 ASCEND)					[redacted]	[redacted]	[redacted]	£3,263,138.3*
Cost-utility (acalabrutinib MAIC 2 ELEVATE-RR)					[redacted]	[redacted]	[redacted]	Dominant

Scenario	Zanubrutinib versus ibrutinib				Zanubrutinib versus acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER(£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cost-utility (acalabrutinib MAIC 2 ASCEND)					[redacted]	[redacted]	[redacted]	£340,034.23*
Cost-utility (acalabrutinib mean increment costs and mean incremental QALYs using ASCEND/ELEVATE-RR)					[redacted]	[redacted]	[redacted]	Dominant

Source: CS, Table 125[6]
*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib
Abbreviations: AE = Adverse event; BTKi = Bruton tyrosine kinase inhibitor; CS = Company submission; ICER = Incremental cost-effectiveness ratio; IRC = Independent review committee; LYG = Life year gained; MAIC = Matching-adjusted indirect comparison; OS = Overall survival; PFS = Progression-free survival; QALY = Quality-adjusted life year; R/R = Relapsed or refractory; TTTD = Time-to-treatment discontinuation.

Table 5.8: Summary of scenario analyses results for zanubrutinib versus ibrutinib and acalabrutinib - probabilistic (n=1,000 iterations)

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base-case	[redacted]				[redacted]			
No Discounting	[redacted]				[redacted]			

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
High Discount rates (6%)	[redacted]				[redacted]			
December 2020 data cut for PFS and OS	[redacted]				[redacted]			
PFS endpoint (IRC)	[redacted]				[redacted]			
PFS curve for zanubrutinib (Gompertz)	[redacted]				[redacted]			
OS curve for zanubrutinib (Exponential)	[redacted]				[redacted]			
Exclude wastage	[redacted]				[redacted]			
Exclude AE costs	[redacted]				[redacted]			
Use TTTD data for zanubrutinib and ibrutinib	[redacted]				[redacted]			
Apply AE impact to QALYs	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	Dominant
Cost-utility (Ibrutinib ALPINE extrapolation)	[redacted]	[redacted]	[redacted]	Dominant				

Scenario	Zanubrutinib vs ibrutinib				Zanubrutinib vs acalabrutinib			
	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cost-utility (acalabrutinib MAIC 1 ELEVATE-RR)					[redacted]	[redacted]	[redacted]	Dominant
Cost-utility (acalabrutinib MAIC 1 ASCEND)					[redacted]	[redacted]	[redacted]	1,674,256.4*
Cost-utility (acalabrutinib MAIC 2 ELEVATE-RR)					[redacted]	[redacted]	[redacted]	Dominant
Cost-utility (acalabrutinib MAIC 2 ASCEND)					[redacted]	[redacted]	[redacted]	341,061.85*
Cost-utility (acalabrutinib mean increment costs and mean incremental QALYs using ASCEND/ELEVATE-RR)					[redacted]	[redacted]	[redacted]	Dominant

Source: CS, Table 126[6]

*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib Abbreviations: AE = Adverse event; BTKi = Bruton tyrosine kinase inhibitor; CS = Company submission; ICER = Incremental cost-effectiveness ratio; IRC = Independent review committee; LYG = Life year gained; MAIC = Matching-adjusted indirect comparison; OS = Overall survival; PFS = Progression-free survival; QALY = Quality-adjusted life year; R/R = Relapsed or refractory; TTTD = Time-to-treatment discontinuation.

EAG comment: Overall, the EAG is satisfied with the exploration of uncertainty in model parameters undertaken by the company. However, there are few points the EAG would like to raise in addition to the points previously raised (see Section 5.1.1.2).

- Considering the mean age ([redacted] years) of the patients in the model and their reasonable life expectancy, it would be good to see the impact in cost savings of reducing the time horizon to 10 years and 15 years in the summary of scenario analyses results tables.

5.2.1.3 Deterministic sensitivity analysis

The DSA presented in the CS (Section B.3b.11.2) states that the results were most sensitive to the parameters used in Weibull models to project PFS for zanubrutinib and the cost of subsequent treatments.[6] The DSA results are summarised in Tables 5.9 (zanubrutinib versus ibrutinib) and 5.10 (zanubrutinib versus acalabrutinib). Tornado plots were used to visualise the DSA results (see Figures 5.5 and 5.6).

Table 5.9: DSA results (incremental costs) for zanubrutinib versus ibrutinib in patients with R/R CLL

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Weibull model to project PFS for zanubrutinib	[redacted]	[redacted]
Cost of subsequent treatments modelled as one-off cost following therapy with zanubrutinib	[redacted]	[redacted]
Cost of subsequent treatments modelled as one-off cost following therapy with ibrutinib	[redacted]	[redacted]
Scale for Weibull model to project PFS for zanubrutinib	[redacted]	[redacted]
Cost of AEs per cycle with ibrutinib	[redacted]	[redacted]
Cost of AEs per cycle with zanubrutinib	[redacted]	[redacted]
Intercept for Weibull model to project OS for zanubrutinib	[redacted]	[redacted]
Scale for Weibull model to project OS for zanubrutinib	[redacted]	[redacted]
Disease management cost per cycle progression-free state	[redacted]	[redacted]

Source: CS, Table 122[6]
Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; OS = Overall survival; PFS = Progression-free survival; R/R = Relapsed or refractory.

Table 5.10: DSA results (incremental costs) for zanubrutinib versus acalabrutinib in patients with R/R CLL

Parameter name	Lower incremental costs	Upper incremental costs
Intercept for Weibull model to project PFS for zanubrutinib	[redacted]	[redacted]
Cost of subsequent treatments modelled as one-off cost following therapy with zanubrutinib	[redacted]	[redacted]

Cost of subsequent treatments modelled as one-off cost following therapy with acalabrutinib	[redacted]	[redacted]
Scale for Weibull model to project PFS for zanubrutinib	[redacted]	[redacted]
Cost of AEs per cycle with acalabrutinib	[redacted]	[redacted]
Cost of AEs per cycle with zanubrutinib	[redacted]	[redacted]
Intercept for Weibull model to project OS for zanubrutinib	[redacted]	[redacted]
Scale for Weibull model to project OS for zanubrutinib	[redacted]	[redacted]
Disease management cost per cycle progression-free state	[redacted]	[redacted]

Source: CS, Table 123[6]
Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; OS = Overall survival; PFS = Progression-free survival.

Figure 5.5: Tornado plot of DSA results (incremental costs) for zanubrutinib versus ibrutinib in patients with R/R CLL

Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; OS = Overall survival; PFS = Progression-free survival; R/R = Relapsed or refractory.

Figure 5.6: Tornado plot of DSA results (incremental costs) for zanubrutinib versus acalabrutinib in patients with R/R CLL

Abbreviations: AE = Adverse event; CLL = Chronic lymphocytic leukaemia; DSA = Deterministic sensitivity analysis; OS = Overall survival; PFS = Progression-free survival; R/R = Relapsed or refractory.

EAG comment: The EAG is satisfied with the DSA and the presentation of results.

5.2.2 Benefits not captured in the QALY calculation

Please refer to Section 5.1.3 of the EAG report.

5.2.3 Severity of the condition

The company did not include a severity analysis in the CS.

5.2.4 Model validation

5.2.4.1 Face validity assessment and technical verification

The company followed the same process for face validity assessment and technical verification for the R/R CLL model that was undertaken for the untreated CLL model (see Section 5.1.5.1)

EAG comment: Overall, the EAG was satisfied with the steps taken for face validation and technical verification

5.2.4.2 Comparison with external data

Similar steps, to the untreated CLL model, were undertaken by the company to validate the R/R CLL model (see Section 5.1.5.2). However, the company clinical trials in R/R CLL (ASCEND and RESONATE) were used to provide external validity to the modelled survival outputs (PFS and OS) for modelled BTKis.[6] The company argue that the outputs for PFS and OS align closely with the clinical trial data. This is reported in Section B.3b.13 of the CS.[6]

EAG comment: The EAG is concerned that the Weibull model may present a pessimistic scenario for OS and PFS over the long-term, which is not captured by comparisons with data over a < 10 years period. The EAG and the company explored the impact of alternative PFS and OS assumption, considering that the partitioned survival structure used for the R/R population is sensitive assumptions made about survival.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The company performed one SLR searching for clinical and economic data. From the evidence obtained in the SLR, two separate economic models were developed for the untreated CLL population and the R/R CLL population, and the EAG analysed them individually. Section 6.1 provides the conclusions from the assessment the EAG made of the SLR; Section 6.2 presents the conclusions from the EAG analysis on the cost-effectiveness evidence presented by the company for the untreated CLL population; and Section 6.3 presents the conclusions to the EAG cost-effectiveness analysis for the R/R CLL population.

6.1 Conclusions from the EAG assessment of the cost-effectiveness literature searches performed by the company

The company undertook one SLR and applied filters to identify potential studies with economic data across both the untreated CLL and the R/R CLL populations. The EAG has concerns about having only a single literature search across multiple databases, alterations to validated study design filters, and a limited search criteria for the intervention which can affect the ability of the SLR to capture all available relevant literature. Likewise, the EAG is unable to verify the potentially relevant records that may have been missed due to the automatic mapping performed by Embase.com. Furthermore, limitations in the terms searched and the databases used to derive HSUV data, made the EAG question the comprehensiveness and validity of the searches performed by the company.

6.2 Exploratory and sensitivity analyses undertaken by the EAG in the untreated CLL population

This section describes the EAG base-case and scenario analyses conducted on both the EAG and the company base-case analyses. The EAG base-case and scenario analyses use the company's economic model for the untreated CLL population and adopts alternative assumptions.

6.2.1 EAG base-case

Table 6.1 summarises the key issues related to the cost-effectiveness, categorised according to the sources of uncertainty defined by Grimm et al (2020).[92]

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g. a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost-effectiveness and whether it is reflected in the EAG base-case, as well as additional evidence or analyses that might help resolve key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous

sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016).[93]

1. Fixing errors (FE): correcting the model where the company's submitted model was unequivocally wrong
2. Fixing violations (FV): correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to
3. Matters of judgement (MJ): amending the model where the EAG considers that reasonable alternative assumptions are preferred

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results, plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case.

No errors were found in the untreated economic model file. However, the EAG consider the assumption on non-inferiority to be unjustified and hence consider the CMA approach adopted by the company to be a violation of accepted best practice.[41] The EAG base-case and scenario analyses were undertaken to assess the impact of alternative assumptions on the cost-effectiveness results using a CUA approach.

6.2.1.1 Fixing errors

No errors were identified by the EAG.

6.2.1.2 Fixing violations

Description: The company used a CMA approach to model the decision problem, over a CUA in their base-case (see Sections 3.4, 4.3.6.2, and 4.4.6.2).

Driven by the large uncertainties around the relative effectiveness between acalabrutinib and zanubrutinib, and the lack of evidence to support non-inferiority for zanubrutinib in all key outcomes for the untreated CLL population as detailed in Section 3.4 and Section 4.3.6.2 and the uncertainty in the data used to inform the untreated "high-risk" CLL subpopulation analyses, the EAG considers that a CUA is a more appropriate approach for its base-case.[41] A CUA approach was adopted by the company in scenario analyses (see Section 5.1.1.2). The EAG critiqued the approach presented by the company (see Section 4.3.2.1) and considers alternative assumptions which maximise all the data available and would produce more robust estimates of cost-effectiveness (see Section 6.2.1.2).

How this violation was addressed by the EAG: Unlike the approach employed by the company in Scenarios 15-21 (Section 5.1.1), the EAG did not apply the HR estimates of PFS directly into the zanubrutinib parametric TTP curves to model the comparator TTP curves. Instead, the EAG applied the HR estimates of OS and PFS to modelled PrePS and TTP curves as follows:

I. The HR estimate for OS from the MAIC between SEQUOIA[29] and ELEVATE-TN,[34] Model 1, was applied to zanubrutinib PrePS to derive the PrePS curve of acalabrutinib. The HR estimate for OS from the ALPINE trial[30] was used on the zanubrutinib PrePS curve to model ibrutinib PrePS.
II. The TTP from zanubrutinib and the PrePS for acalabrutinib and ibrutinib were combined to generate PFS for each comparator respectively.
III. The HR estimate for PFS from the MAIC between SEQUOIA[29] and ELEVATE-TN,[34] Model 1, was applied to the acalabrutinib PFS curve, to then derive TTP for acalabrutinib. Similarly,

the HR estimate for PFS from the ALPINE trial was used on the PFS curve of ibrutinib to derive TTP respectively.[30]

The EAG acknowledges there were a number of caveats with this approach. The first caveat was the assumption that relative hazard estimates of OS can be applied to the current SEQUOIA[29] PrePS data; the EAG adopts this assumption as the current follow up of the trial data is short and the number of OS death events was relatively low [redacted]. [redacted] The EAG acknowledges that OS and PrePS are distinct endpoints, yet given the current absence of evidence this assumption makes the most of the available data while delivering a potentially conservative scenario. The EAG also presents a scenario where the impact of excluding OS HR estimates on the cost-effectiveness results is explored.

This approach also assumed that a partitioned-survival approach was appropriate to derive TTP from PFS. Although this was a strong assumption, the EAG again considers this approach to be the best use of all the data presented, considering the paucity of evidence for this population. Further limitations of this approach include the assumption of constant relative hazards over time, and that treatment effects have a lifetime duration, which add to the uncertainty around the results presented.

An alternative scenario using Model 2 HR estimated from the MAIC between SEQUOIA[29] and ALPINE was also presented by the EAG as a less favourable comparison between zanubrutinib and acalabrutinib.

6.2.1.3 Matters of judgement

An overview of the key issues related to the cost-effectiveness is presented in Table 6.1.

Table 6.1: Overview of key issues related to the cost-effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Use of a CMA as the company's base-case	3.4/4.3.6.2/4.4.6.2	Transparency; Imprecision	A CUA using HR estimates from different MAIC models	+/-	Explored as the EAG base-case	Better quality evidence/data for the relative efficacy between zanubrutinib and acalabrutinib
Uncertainty in the utility estimates used in the company's economic model	4.3.8/4.4.8	Transparency	Utility data derived from the SEQUOIA trial[29]	+	Explored in scenario analyses 2-3	Utility data was not recorded for Cohort 2 of SEQUOIA,[29] therefore differences HRQoL across patients with del17p and/or TP53 mutation are unknown.
Immaturity in the trial data and parametric survival functions	4.3.6.1/4.4.6.1	Imprecision; Unavailability	Alternative distribution functions used to model TTP	+	Explored in scenario analyses 6-7	SEQUOIA data from cut-off dates beyond May 2021 could diminish some of the uncertainty. Longer term data in this population is lacking, which could better inform the selection of parametric models
Uncertainty in untreated CLL subgroups based on the presence of del17p or TP53 mutation	4.3.3	Unavailability	Subgroup analysis using SEQUOIA data separated by presence of del17p or TP53 mutation	+/-	Explored in EAG sub-group analyses 1-4	A comparison of KM data across arm A and arm C of SEQUOIA ideally over more mature data.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator;
[b] Explored.
Abbreviations: CLL = Chronic lymphocytic leukaemia; CMA = cost-minimisation analysis; CUA = Cost-utility analysis; EAG = External assessment group; HR = Hazard rate; HRQoL = Health-related quality of life; KM = Kaplan Maier; MAIC = Matching-adjusted indirect comparison.

1. Uncertainty in the utility estimates used in the company's economic model (Section 4.3.8)

The CUA presented by the company as a scenario analysis (see Section 5.1.3) utilised previously used utility values from NICE TA689[64] for the PF and PD health states, as utilities obtained from SEQUOIA[29] were argued to lack face validity.[6] PF and PD health state utility values from the CS base-case were maintained in the EAG base-case; however, the EAG undertook a scenario analysis using utility values from SEQUOIA.[29]

The EAG was concerned about the source used to derive the utility value for the PD state (see Section 4.3.8.2); therefore, an EAG scenario analysis used the difference in mean utility values between PF and PD obtained from SEQUOIA[29] as a PD disutility and applied this disutility to the PF utility value in the CS base-case to derive and alternative utility value for the PD health state only.

2. Immaturity in the trial data and parametric survival functions (Section 4.3.6.1)

The CS base-case selected a Generalised Gamma distribution to extrapolate TTP and PrePS over the long-term. This distribution gave the most optimistic predictions of TTP relative to the other distributions presented; therefore, the company presented a scenario analysis using a log-normal and an exponential distribution (see section 5.1.1.2). The EAG considered it informative to present the impact of more pessimistic extrapolations on the EAG base-case results.

The Weibull distribution was considered the most pessimistic distribution that still judged clinically feasible, while the Lognormal distribution was considered a midpoint between the Weibull and Generalised Gamma distributions. The EAG did not reject the use of the Generalised Gamma distribution in its own base-case, as despite having the most optimistic predictions for TTP, it was still likely to be pessimistic relative to clinical practice according to expert opinion sought by the EAG.

3. Uncertainty around the effectiveness of zanubrutinib across the untreated "high-risk" CLL subpopulation, and the "unfit" CLL subpopulation (Section 4.3.3)

The company presented an independent visual assessment of arm A (untreated "unfit" cohort) and arm C ("high-risk" cohort) of KM data for TTP and PrePS.[65] However, the EAG was not able to assess whether there was a clinically meaningful difference in the risk of progression across both populations from this analysis alone. Therefore, the EAG is still uncertain about the appropriateness of pooling data together these two populations. However, the EAG acknowledges that due to the immaturity of the data, there may be additional issues and uncertainties to consider when comparing the KM data of the two subpopulations, specifically around mortality related outcomes.

The company presented eight scenarios using the CS base-case model (see Section 5.1.1.2) to assess the cost-effectiveness evidence between for the "unfit" and the "high-risk" populations independently using a CMA approach, using a CUA approach with estimates of PFS from the ELEVATE-TN MAIC across both populations, and a CUA approach for the "high-risk" population using estimates from the ELEVATE-RR MAIC and the naïve comparison with Mato *et al.,* (2018).[5]

The EAG undertook a sub-group analysis of the EAG base-case CUA model for untreated "high-risk" CLL. Parametric survival data for TTP and PrePS were derived from arm C in SEQUOIA,[29] and MAIC results from Model 1 comparing ALPINE[88] and ELEVATE-RR[36] (INV-assessed) were used to model the survival curves for acalabrutinib in this population. Less favourable relative effectiveness estimates for acalabrutinib in the "high-risk" subpopulations were also explored using the MAIC results in Model 2 comparing ALPINE[88] and ASCEND.[35]

To model ibrutinib in the EAG base-case model, PFS HR estimates for INV-assessed outcomes in patients with del17p and/or TP53 mutation, reported in the ALPINE trial in the CS,[6] were combined with the PFS survival curves derived from arm C of SEQUOIA[29] to generate the respective TTP curve.

To model the untreated "unfit" CLL subpopulation in the EAG base-case model, parametric survival curves from arm A of SEQUOIA were combined with results from the MAIC between SEQUOIA[29] and ELEVATE-TN,[34] Model 1. Less favourable relative effectiveness estimates for acalabrutinib in the "non high-risk" subpopulation were obtained from the MAIC results of Model 2 comparing SEQUOIA and ELEVATE-TN.[29,34]

4. The company used a simple average between the parametric survival curves from the SEQUOIA arms treated with zanubrutinib (arm A and arm C), and the arm treated with BR (arm B) to model PrePS (see Section 4.3.6.1.2)[6]

The EAG acknowledged that, given the immaturity of survival data in some trials, pooling patient data across comparator arms (after demonstrating evidence of no difference between them) is a method that has been used in previous NICE appraisals (e.g. NICE TA810[94]). However, the primary concern for the EAG was the methodology used by the company, as rather than pooling from patient data, the company derived the parametric curves for each patient group (zanubrutinib (arm A and arm C), and BR (arm B)) and then applied a simple average across both parametric survival extrapolations. To partially address this, the EAG used the PrePS curves derived from patients treated with zanubrutinib only arm (A and arm C pooled) in the EAG base-case.

6.2.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.2.2.1 List of exploratory scenario analyses

This section describes the scenario and sensitivity analyses conducted by the EAG. The EAG conducted ten scenario analyses not conducted by the company. All these scenario and sensitivity analyses are described below.

1. Pessimistic acalabrutinib HR estimates (Section 4.3.6.2.1)

The MAIC performed by the company presented two models with different estimates for PFS and OS HRs between zanubrutinib and acalabrutinib for the untreated CLL population. Model 1 estimates were used in the EAG base-case, while Model 2 estimates of PFS and OS were used as a pessimistic scenario for zanubrutinib (see Section 3.3.1 and Section 4.3.6.2).

2. Utility estimates from SEQUOIA (Section 4.3.8)

The EAG used utility values from the SEQUOIA trial[29] for PF and PD health states to explore uncertainty in the utility values used in the company base-case.

3. Alternative utilities for post-progression patients (Section 4.3.8)

The EAG explored the impact of varying the utilities for patients in the progressed disease health state due to the uncertainty in values used by the company (see Section 4.3.8.2). The EAG estimated a progression disutility using the difference between the PF and PD health state utility values derived from the SEQUOIA trial.[29] The derived disutility was applied to the PF health state utility value used in the company CUA scenario analysis to generate the alternative PD health state utility value.

4. Equivalent adverse events profile across all arms (Section 4.3.7)

To explore the impact of the different AE incidences across comparator arms, the incidence values for zanubrutinib from arm A and arm C in the SEQUOIA trial[29] were applied across the comparator arms in the model.

5. R/R CLL adverse events incidence (Section 4.3.7)

The incidence values used in the base-case were replaced by the incidence values used in the R/R CLL model, particularly for zanubrutinib and ibrutinib, as these were sourced from the ALPINE trial offering a direct comparison between both arms.[88] However, the EAG acknowledges that the AE profile can vary across untreated CLL and R/R CLL population, therefore this assumption was not adopted as part of the EAG base-case.

6. Pessimistic TTP survival curves using the Weibull distribution (Section 4.3.6)

The EAG acknowledges that all the extrapolated survival models from SEQUOIA potentially present pessimistic predictions of TTP for the untreated CLL population.[29] However, in order to test the impact of alternative survival curves on the economic model, the Weibull distribution was chosen as the most pessimistic scenario still within clinical feasibility. The Weibull distribution was applied to both TTP and PrePS.

7. Less pessimistic TTP survival curves using the Log-normal distribution (Section 4.3.6)

Due to the Log-normal distribution presenting the best statistical fit to TTP data from SEQUOIA[29] and representing a midpoint between the Weibull and the Generalised Gamma, this distribution was explored as a scenario analysis. The Log-normal distribution was applied to both TTP and PrePS.

8. Less pessimistic PPS using a Gen. Gamma distribution (Section 4.3.6)

PPS was modelled after a parametric OS curve from the MURANO trial[51] following an Exponential distribution which provided the most pessimistic survival over the long-term relative to the other distributions. While varying the assumptions around PPS would not have an impact on incremental results from the company's CMA, under the CUA proposed by the EAG this might not be the case. The Log-normal distribution was used to model the PPS curve as a less pessimistic scenario analysis.

9. Less pessimistic 2L treatment duration using an Exponential distribution (Section 4.3.6)

Treatment discontinuation for 2L therapy after the intervention was modelled from the PFS curve of the MURANO trial[51] following a Gompertz distribution which produced a pessimistic scenario of treatment duration (i.e., a higher risk of treatment discontinuation relative to other models) over the long-term. The impacts of a more optimistic assumption were explored in a scenario using an Exponential distribution instead.

10. A time horizon of 15 years (Section 5.1.1)

The EAG considers the 30-year lifetime horizon of the CS base-case to be appropriate to represent the decision problem. However, given the age of the population a shorter time horizon was used to explore the medium-term estimates of cost-effectiveness for zanubrutinib.

11. CUA excluding OS HR estimates

The EAG base-case model makes the assumption that OS HRs obtained from the MAIC analyses were applicable to PrePS data from SEQUOIA.[6] As this has the potential to be a strong assumption over the long-term, the EAG explored an alternative CUA approach using only PFS HR estimates from the MAIC to predict survival in the comparator arms.

6.2.3 EAG subgroup analyses

This section describes the subgroup analyses conducted by the EAG. The EAG conducted four subgroup analysis in the untreated CLL model: 1) "high-risk" patients; 2) unfavourable scenario for "high-risk" patients using the highest HR estimates for zanubrutinib versus acalabrutinib from the MAIC analysis results; 3) "unfit" patients; 4) unfavourable scenario for "unfit" patients using the highest HR estimates for zanubrutinib versus acalabrutinib from the MAIC results. These subgroup analyses are described in more detail in Section 6.2.3.1.

6.2.3.1 List of subgroup analyses

1. "High-risk" patients

Parametric survival curves for TTP and PrePS from arm C from SEQUOIA[29] were applied to the EAG base-case to undertake a CUA comparing zanubrutinib versus acalabrutinib and ibrutinib in the untreated "high-risk" CLL subpopulation. The HR values for zanubrutinib versus acalabrutinib obtained

from the MAIC using INV-assessed estimates from ALPINE[88] and ELEVATE-RR in Model 2[36] (see Section 3.3.2.5 and Section 4.3.6.2), were used to model relative effectiveness against acalabrutinib.

The relative hazards between zanubrutinib and ibrutinib were modelled using overall OS HR estimates from ALPINE[88] for PrePS, while the PFS HR estimates for the INV-assessed "high-risk" population outcomes of ALPINE reported in Section B.3a.3.4.2 of the CS[6] were used to adjust TTP.

2. "High-risk" patients with pessimistic relative effectiveness estimates against acalabrutinib

This EAG scenario used parametric extrapolations for arm C from SEQUOIA[29] with relative hazards from Model 2 the MAIC between ALPINE versus ASCEND[35] (see Section 3.3.2.5 and Section 4.3.6.2) to model PrePS and TTP in acalabrutinib. These estimates represent lower HRs relative to the base-case and hence a lower effectiveness for zanubrutinb versus acalabrutinib.

3. "Unfit" patients

To model this scenario, the EAG used parametric extrapolations of TTP and PrePS from patient data in arm A from the SEQUOIA trial[29] The relative risk results against acalabrutinib from Model 1 in the MAIC between SEQUOIA[29] and ELEVATE-TN[34] were used to model TTP and PrePS in the acalabrutinib arm.

4. "Unfit" patients with pessimistic relative effectiveness estimates against acalabrutinib

To model this scenario, the EAG used parametric extrapolations of TTP and PrePS derived from the patient data in arm A from the SEQUOIA trial[29] The HR estimates of Model 2 in the MAIC between SEQUOIA[29] and ELEVATE-TN[34] were used to model TTP and PrePS in the acalabrutinib arm (see Section 3.3.1.5). These estimates represent lower HRs relative to the base-case and hence lower effectiveness for zanubrutinib versus acalabrutinib.

6.2.4 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.4.1 The EAG base-case, scenario and subgroup analyses

In section 6.2.1, the features of the EAG base-case were presented, which was based on various changes compared to the company base-case relating to both fixing of errors and matters of judgement (MJ). The results of these changes in the deterministic EAG base case model are show in Tables 6.2 and 6.3 for the comparison of zanubrutinib versus acalabrutinib and zanubrutinib versus ibrutinib respectively.

Table 6.4 lists the scenarios applied to the EAG base-case, Table 6.5 presents the scenario results for zanubrutinib versus acalabrutinib, and Table 6.6 presents the scenario results for zanubrutinib versus ibrutinib.

Table 6.7 lists the subgroup analyses from the EAG base-case, Table 6.8 presents the subgroup results for zanubrutinib versus acalabrutinib, and Table 6.9 presents the subgroup results for zanubrutinib versus ibrutinib.

Table 6.2: Deterministic EAG base-case results (unless otherwise stated) – zanubrutinib versus acalabrutinib

Comparators	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			
CS base-case – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			
Mortality only from BTKi data					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			
CS base-case – CUA					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			
EAG proposed CUA					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			
EAG base-case – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			
EAG base-case – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Acalabrutinib	[redacted]	[redacted]			

Abbreviations: BTKi = Burton tyrosine kinase inhibitor; CS = Company submission; CUA = Cost-utility analysis; EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life year.

Table 6.3: Deterministic EAG base-case results – zanubrutinib versus ibrutinib

Comparators	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
CS base-case – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
Mortality only from BTKi data					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
CS base-case – CUA					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
EAG proposed CUA					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
EAG base-case – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
EAG base-case – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			

Abbreviations: BTKi = Burton tyrosine kinase inhibitor; CS = Company submission; CUA = Cost-utility analysis; EAG = Evidence Assessment Group; ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life year.

Table 6.4: List of EAG scenario analyses in the untreated CLL model

Scenario	Scenario description
1	Pessimistic acalabrutinib HR estimates (Section 4.3.6.2.1): Model 2 of the untreated CLL MAIC presented higher risk ratios for zanubritib: PFS HR vs acalabrutinib: [redacted]; OS HR vs acalabrutinib: [redacted]
2	Utility estimates from SEQUOIA (Section 4.3.8): SEQUOIA-derived utilities: PF = [redacted]; PD = [redacted][29]
3	Alternative utilities for post-progression patients (Section 4.3.8): SEQUOIA-derived PD disutility applied to base-case PF: PD = [redacted][29]
4	Equivalent adverse events profile across all arms (Section 4.3.7): Incidence values in all arms equivalent to the zanubrutinib arm of SEQUOIA[29]
5	R/R CLL adverse events incidence (Section 4.3.7): AE incidence values taken from the R/R CLL model on each respective arm
6	Pessimistic TTP survival curves using the Weibull distribution (Section 4.3.6):

	Higher risk of progression relative to alternative models
7	Less pessimistic TTP survival curves using the Log-normal distribution (Section 4.3.6): Increased risk of progression relative to the base-case
8	Less pessimistic PPS using a Gen. Gamma distribution (Section 4.3.6): Lower risk of death at the progressed disease stage relative to the base-case
9	Less pessimistic 2L treatment duration using an Exponential distribution (Section 4.3.6): Lower risk of 2L treatment discontinuation
10	A time horizon of 15 years (5.1.1)
11	CUA excluding OS HR estimates
Abbreviations: AE = Adverse events; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; HR = Hazard rates; PD = Progressed disease; PF = Progression-free; PPS = Post-progression survival; 2L = Second line.	

Table 6.5: Deterministic results of EAG scenario analyses (zanubrutinib versus acalabrutinib)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	N/A	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 1	PFS HR vs acalabrutinib: [redacted]; OS HR vs acalabrutinib: [redacted]	PFS HR vs acalabrutinib: [redacted]; OS HR vs acalabrutinib: [redacted]	[redacted]	[redacted]	£13,350,239*
Scenario 2	EAG base-case utilities: PF = 0.783; PD = 0.6	SEQUOIA-derived utilities: [redacted][29]	[redacted]	[redacted]	£28,634,340*
Scenario 3	EAG base-case PD utilities from Holzner *et al.*, (2004)[82]	SEQUOIA-derived PD disutility applied to base-case PF: [redacted][29]	[redacted]	[redacted]	£31,266,742*
Scenario 4	EAG base-case AE incidence	SEQUOIA AE incidence across all arms[29]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 5	EAG base-case AE incidence	AE incidence used in the R/R CLL model	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 6	Gen. Gamma distribution for TTP and PrePS	Weibull distribution for TTP and PrePS	[redacted]	[redacted]	Zanubrutinib Dominant

Scenario 7	Gen. Gamma distribution for TTP and PrePS	Log-normal distribution for TTP and PrePS	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 8	MURANO OS Exponential[51]	MURANO OS Gen. Gamma[51]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 9	MURANO PFS Gompertz[51]	MURANO PFS Exponential[51]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 10	Full lifetime horizon (30 years)	15-year time horizon	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 11	PFS and OS HR estimates applied on pre-progression data from SEQUOIA	PFS HR estimates only	[redacted]	[redacted]	Zanubrutinib Dominant

* ICER was estimated for acalabrutinib as it was more costly and more effective

Abbreviations: AE = Adverse events; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; HR = Hazard rates; ICER = Incremental cost-effectiveness ratio; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PPS = Post-progression survival; PrePS = PreProgression survival; QALYs = Quality-adjusted life years; R/R = Relapsed or refractory; TTP = Time-to-progression; 2L = Second line.

Table 6.6: Deterministic results of EAG scenario analyses (zanubrutinib versus ibrutinib)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	N/A	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 1	PFS HR vs acalabrutinib: [redacted]; OS HR vs acalabrutinib: [redacted]	PFS HR vs acalabrutinib: [redacted]; OS HR vs acalabrutinib: [redacted]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 2	EAG base-case utilities: PF = 0.783; PD = 0.6	SEQUOIA-derived utilities: [redacted][29]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 3	EAG base-case PD utilities from Holzner et al.,, 2004[82]	SEQUOIA -derived PD disutility applied to base-case PF: [redacted][29]	[redacted]	[redacted]	Zanubrutinib Dominant

Scenario 4	EAG base-case AE incidence	SEQUOIA AE incidence across all arms[29]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 5	EAG base-case AE incidence	AE incidence used in the R/R CLL model	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 6	Gen. Gamma distribution for TTP and PrePS	Weibull distribution for TTP and PrePS	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 7	Gen. Gamma distribution for TTP and PrePS	Log-normal distribution for TTP and PrePS	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 8	MURANO OS Exponential [51]	MURANO OS Gen. Gamma[51]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 9	MURANO PFS Gompertz[51]	MURANO PFS Exponential[51]	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 10	Full lifetime horizon (30 years)	15-year time horizon	[redacted]	[redacted]	Zanubrutinib Dominant
Scenario 11	PFS and OS HR estimates applied on pre-progression data from SEQUOIA	PFS HR estimates only	[redacted]	[redacted]	Zanubrutinib Dominant

Abbreviations: AE = Adverse events; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; HR = Hazard rates; ICER = Incremental cost-effectiveness ratio; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PPS = Post-progression survival; PrePS = PreProgression survival; QALYs = Quality-adjusted life years; R/R = Relapsed or refractory; TTP = Time-to-progression; 2L = Second line.

Table 6.7: List of EAG subgroup analyses in the untreated CLL model

Scenario	Subgroup description
1	"High-risk" patients: TTP and PrePS survival extrapolations based on pooled data from arm C only of SEQUOIA;[29] PFS and OS MAIC results from ALPINE vs ELEVATE-RR Model 1
2	"High-risk" patients with pessimistic relative effectiveness versus acalabrutinib: TTP and PrePS survival extrapolations based on pooled data from arm C only of SEQUOIA;[29] PFS and OS MAIC results from ALPINE vs ASCEND Model 2
3	"Unfit" patients: TTP and PrePS survival extrapolations based on pooled data from arm A only of SEQUOIA;[29] PFS and OS MAIC results from SEQUOIA vs ELEVATE-TN Model 1
4	"Unfit" patients with pessimistic relative effectiveness estimates against acalabrutinib: TTP and PrePS survival extrapolations based on pooled data from arm A only of SEQUOIA;[29] PFS and OS MAIC results from SEQUOIA vs ELEVATE-TN Model 1

Abbreviations: CLL = Chronic lymphocytic leukaemia; EAG = Evidence Assessment Group.

Table 6.8: Deterministic results of EAG subgroup analyses (zanubrutinib versus acalabrutinib)

Subgroup	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	NA	[redacted]	[redacted]	Zanubrutinib Dominant
1	TTP and PrePS survival extrapolations based on pooled data from arm A and arm C of SEQUOIA[29]	TTP and PrePS survival extrapolations based on pooled data from arm C only of SEQUOIA;[29] PFS and OS MAIC results from ALPINE vs ELEVATE-RR Model 1	[redacted]	[redacted]	Zanubrutinib Dominant
2	TTP and PrePS survival extrapolations based on pooled data from arm A and arm C of SEQUOIA[29]	TTP and PrePS survival extrapolations based on pooled data from arm C only of SEQUOIA;[29] PFS and OS MAIC results from ALPINE vs ASCEND Model 2	[redacted]	[redacted]	Zanubrutinib Dominant
3	TTP and PrePS survival extrapolations based on pooled data from arm A and arm C of SEQUOIA[29]	TTP and PrePS survival extrapolations based on pooled data from arm A only of SEQUOIA;[29] PFS and OS MAIC results from SEQUOIA vs ELEVATE-TN Model 1	[redacted]	[redacted]	£15,387,982*

4	TTP and PrePS survival extrapolations based on pooled data from arm A and arm C of SEQUOIA[29]	TTP and PrePS survival extrapolations based on pooled data from arm A only of SEQUOIA;[29] PFS and OS MAIC results from SEQUOIA vs ASCEND-TN Model 2	[redacted]	[redacted]	£817,539*

* ICER was estimated for acalabrutinib as it was more costly and more effective.
Abbreviations: AE = Adverse events; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; HR = Hazard rates; ICER = Incremental cost-effectiveness ratio; MAIC = Matching-adjusted indirect comparison; NA = Not applicable; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PPS = Post-progression survival; PrePS = PreProgression survival; QALYs = Quality-adjusted life years; R/R = Relapsed or refractory; TTP = Time-to-progression; 2L = Second line.

Table 6.9: Deterministic results of EAG subgroup analyses (zanubrutinib versus ibrutinib)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	NA	[redacted]	[redacted]	Zanubrutinib Dominant
1	TTP and PrePS survival extrapolations based on pooled data from arm A and arm C of SEQUOIA[29]	TTP and PrePS survival extrapolations based on pooled data from arm C only of SEQUOIA;[29] HR for PFS for ibrutinib from the CS, section B.3a.3.4.2 [redacted]	[redacted]	[redacted]	Zanubrutinib Dominant
2	TTP and PrePS survival extrapolations based on pooled data from arm A and arm C of SEQUOIA[29]	TTP and PrePS survival extrapolations based on pooled data from arm C only of SEQUOIA; [29] HR for PFS for ibrutinib from the CS, section B.3a.3.4.2 [redacted]	[redacted]	[redacted]	Zanubrutinib Dominant

3	Ibrutinib is only delivered to "high-risk" patients with del17p and/or TP53 mutations, hence it is not a relevant comparator in this subgroup.
4	
Abbreviations: AE = Adverse events; CLL = Chronic lymphocytic leukaemia; CS = Company submission; EAG = Evidence Assessment Group; HR = Hazard rates; ICER = Incremental cost-effectiveness ratio; NA = Not applicable; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PPS = Post-progression survival; PrePS = PreProgression survival; QALYs = Quality-adjusted life years; R/R = Relapsed or refractory; TTP = Time-to-progression; 2L = Second line.	

6.2.5 EAG base-case results for the untreated CLL population

Figure 6.1 illustrates that for all 1,000 iterations of the PSA, zanubrutinib was less costly than both acalabruitin and ibrutinib. In the EAG base-case, zanubrutinib dominated acalabrutinib and had a [redacted] probability of being considered cost-effective at a £20,000 threshold for an additional QALY (Figure 6.2). Zanubrutinib dominated ibrutinib and the probability of zanubrutinib being considered cost-effective was [redacted] at a £20,000 threshold for an additional QALY (Figure 6.2).

The scenarios which had the biggest impact on the EAG base-case were:

- Using more pessimistic HR estimates from Model 2 of the MAIC comparing zanubrutinib versus acalabrutinib, rather than Model 1 (Scenario 1)
- Using a lower disutility estimate derived using data from SEQUOIA (Scenario 3)
- Using a Weibull distribution for TTP and PrePS (Scenario 6)
- Using an Exponential distribution to model PPS (Scenario 8)

Results from the subgroup analysis separated by risk suggested that for the "high-risk" subpopulation with del17p and/or TP53 mutation, zanubrutinib was the dominant intervention compared with either acalabrutinib or ibrutinib. For the "unfit" subgroup comparing only zanubrutinib versus acalabrutinib, zanubrutinib became less costly and less effective, with ICERs for acalabrutinib ranging from £2,788,793 to £15,387,982, using data from ASCEND and ELEVATE-TN respectively to model relative effectiveness.

Figure 6.1: Cost-effectiveness plane for zanubrutinib versus ibrutinib and acalabrutinib

Abbreviations: QALYs = Quality-adjusted life years.

Figure 6.2: Cost-effectiveness acceptability curves for zanubrutinib versus ibrutinib and acalabrutinib

Results from the DSA on the EAG base-case show that the parameters that had the largest impact on costs were:

- The HR estimate for TTP
- The HR estimate for PrePS

- The drug acquisition costs for zanubrutinib, acalabrutinib and ibrutinib
- Intercept and shape parameters of the TTP curve

The parameters that had the largest impact on QALYs from the DSA on the EAG base-case were:

- The HR estimate for TTP
- The HR estimate for PrePS
- The utility value of the PD health state

As shown in Figures 6.3 and 6.4 zanubrutinib was less costly when compared with acalabrutinib and was more effective, in terms of QALYs gained, except when variations in the HR estimates for TTP and PrePS were applied.. When compared with ibrutinib, zanubrutinib remained dominant (i.e. less costly and more effective) in every DSA, as shown in Figures 6.5 and 6.6.

Figure 6.3: Tornado plot: Incremental costs zanubrutinib versus acalabrutinib

Abbreviations: BTK = Bruton tyrosine kinase; PF2SL = Progression-free survival for second-line treatment; PPS = Post-progression survival; PrePS = PreProgression Survival; TTP = Time-to-progression.

Figure 6.4: Tornado plot: Incremental QALYs zanubrutinib versus acalabrutinib

Abbreviations: BTK = Bruton tyrosine kinase; HR = Hazard ratio; PPS = Post-progression survival; PrePS = PreProgression Survival; QALYs = Quality-adjusted life years; TTP = Time-to-progression.

Figure 6.5: Tornado plot: Incremental costs zanubrutinib versus ibrutinib

Abbreviations: BTK = Bruton tyrosine kinase; PF2SL = Progression-free second-line treatment; PPS = Post-progression survival; PrePS = PreProgression Survival; TTP = Time-to-progression.

Figure 6.6: Tornado plot: Incremental QALYs zanubrutinib versus ibrutinib

Abbreviations: BTK = Bruton tyrosine kinase; HR = Hazard ratio; PPS = Post-progression survival; PrePS = PreProgression Survival; QALYs = Quality-adjusted life years; TTP = Time-to-progression.

6.2.6 Conclusions of the cost-effectiveness section for the untreated CLL population

The company undertook one SLR and applied filters to identify studies to inform the clinical effectiveness and cost-effectiveness data presented in the CS. Ten studies were identified on HRQoL and five on costs and healthcare resource use. The company did not use the results of the SLR to inform the structure of the economic model in untreated CLL. Overall, the EAG has concerns that the search terms, databases and filters used were not sensitive enough to capture all potentially relevant data on HRQoL, however the EAG is satisfied with the process the company adopted to select studies from their search results.

The EAG consider that the company complied with the NICE reference; however, the EAG have concerns about the company's justification for undertaking a CMA as their base-case analysis. The assumption of non-inferiority rather no evidence of a difference was made due to limited available data. For zanubrutinib compared with acalabrutinib, this assumption was based on the multiple MAIC analyses comparing zanubrutinib and acalabrutinib where no statistically significant difference was found in the clinical outcomes. For zanubrutinib compared with ibrutinib the results of ALPINE and a naïve comparison with Mato *et al*. (2018)[5] were used to justify non-inferiority against the ibrutinib arm. These data were used to inform the clinical effectiveness parameter estimates under the assumption that R/R was a proxy for untreated "high-risk" CLL. However, the EAG have concerns about this assumption as only about 23% of participants in each arm of ALPINE had del17p and/or TP53 mutation and Mato *et al*., (2018) is an observational retrospective study, where a naïve comparison does not control for potential confounders such as age or IGHV mutation.[5] Also, clinical advice to the EAG suggested that R/R CLL is not a good proxy for "high-risk". Hence there is uncertainty in the generalisability of these results to the untreated "high-risk" CLL population. As the EAG believes there is insufficient evidence and hence uncertainty in the assumption of non-inferiority in untreated CLL. Therefore, a CMA approach was not considered to be the most appropriate method to represent the decision problem. The company did undertake a CUA for both pairwise comparisons as a scenario analysis. The EAG modified the model submitted by the company to present an alternative application of the CUA proposed by the company and improve the accuracy of results. Yet the EAG acknowledges the model relies on strong assumptions and structural uncertainties that could not be incorporated into the EAG base-case.

To model the untreated CLL population, the company presented a three-health state semi-Markov structure. The three mutually exclusive health states consisted of PF, PD, and death. Patients start at the PF state, and can suffer disease progression and move to PD or die; once progressed patients stay at the PD state until they die. Under the CMA approach proposed by the company, assuming that the clinical effectiveness of the comparators was equivalent to zanubrutinib, the semi-Markov structure presented the best use of available evidence. The EAG have no concerns about the model structure for untreated CLL.

The untreated CLL model was comprised of two subgroups 1) "unfit" patients (i.e., patients who would be considered unfit to receive FCR or BR) and 2) "high-risk" patients (i.e., patients with del17p and/or TP53 mutation unsuitable to receive CIT treatment). In the decision problem, acalabrutinib is a suitable treatment for "high-risk" CLL and "unfit" CLL patients, while ibrutinib is only suitable for "high-risk" patients. Data for "unfit" patients were derived from Cohort 1 (arm A) of the SEQUOIA trial[29] which randomised patients to treatment with either zanubrutinib or BR, hence the EAG questions the generalisability of evidence from a potentially 'fit' patient population to the "unfit" subpopulation. The EAG acknowledges that "fitness" is non-binary but based on the company's placement of zanubrutinib

in the patient pathway the EAG have concerns about the data from SEQUOIA being used as a proxy for "unfit" patients. Data for "high-risk" patients were derived from Cohort 2 (arm C) of the SEQUOIA trial.[29] However, the company considered the data to be too immature due to the low number of events, hence, arm A and arm C were pooled together and used to derive the survival parameters for both acalabrutinib and ibrutinib in the untreated CLL model.

The intervention in the untreated CLL model was zanubrutinib administered orally twice daily in the form of two 80 mg capsules for a total 160 mg per administration. Acalabrutinib was a comparator treatment for untreated CLL patients administered orally twice daily at a total 100 mg per administration. Ibrutinib was included as a comparator for untreated CLL ("unfit" and "high-risk") but in practice it is only provided to those who are "high risk" and was administered orally once daily at 420 mg per administration. There was no formal stopping rule modelled for either the intervention or comparator treatments in the CS base-case, which meant that patients were treated until disease progression or death across all treatment arms.

The economic model assumed a lifetime horizon with a 30-year duration. To model patients leaving the PF health state, the model used TTP and PrePS data from SEQUOIA,[29] extrapolated over 30 years by fitting six parametric distributions (Weibull, Log-normal, Log-logistic, Exponential, Generalised Gamma, and Gompertz).

To model TTP, the company pooled patient data across arm A and arm C from SEQUOIA.[29] The EAG is concerned that a preliminary analysis of the differences between the KM curves for arm A and arm C was not performed by the company to justify the appropriateness of pooling these data together. This has important implications for the economic model, as the CMA approach used by the company assumes equivalent survival functions for ibrutinib and acalabrutinib to those of zanubrutinib.

The company derived a parametric survival curve for pooled arm A and arm C data, and a parametric curve for arm B from SEQUOIA,[29] and a PrePS curve was presented as a simple average between both parametric curves. The EAG is concerned that rather than combining data across all three arms at the patient level, the company opted for this approach instead. The risk of mortality in the derived PrePS curves was constrained by the risk of mortality from the general UK population so that it could not fall below the general mortality risk, which the EAG considered appropriate.

The statistical fit of the parametric distributions used for TTP and the PrePS, presented similar levels of goodness of fit but large differences in long-term predictions of survival. To select an appropriate distribution, the company derived PFS curves using the same distributions in both TTP and PrePS and selected the base-case parametric distribution based on clinical expert opinion. The Generalised. Gamma distribution was chosen as the CS base-case distribution for both TTP and PrePS, which also presented the most optimistic predictions of TTP relative to the other distributions. Clinical opinion sought by the EAG considered the TTP predictions of the Generalised Gamma model to still be pessimistic compared to clinical practice.

Once patients move to the PD health state in the model, they were assumed to receive treatment with VenR therapy consisting of venetoclax administered for two years, and rituximab for six 28-day cycles until treatment discontinuation or death. Time to treatment discontinuation and overall survival in the PD health state were modelled from the PFS and the OS curves of the MURANO trial[51] respectively. The selection of the parametric distributions to extrapolate the data from MURANO was based on statistical fit and expert opinion. Although changes in these parameters had no impact on the cost-

effectiveness results under the CMA approach presented by the company, the EAG was concerned about the impact they might have under a CUA approach.

The economic model accounted for ≥ grade 3 AEs that occurred in ≥ 1% of the patient population. AE incidences were derived from SEQUOIA[29] for zanubrutinib, RESONATE-2[31] for ibrutinib, and ELEVATE-TN[34] for acalabrutinib, while utility decrements for each AE were sourced from the published literature. AEs were included only during the first cycle in the model, which had a 28-day duration. The EAG considers this to be an unrealistic assumption for some of the AEs included (e.g. cataracts and hypertension which would take longer than 28 days to resolve). Furthermore, AEs such as cataracts would not necessarily be expected to be treatment-related but rather they might expected given the age of modelled population. Their inclusion raises doubts on the methods used to include AEs in the model. Due to the low frequency and utility decrements obtained, assumptions around AEs had little impact in the company's cost-effectiveness results. Whilst this could be questioned, zanubrutinib was associated with generally fewer AEs than the comparators and hence the EAG consider that this was a conservative assumption for zanubrutinib.

The company presented a CUA as a scenario analysis only, the same HSUVs were applied across intervention and comparator arms, this is in part was justified by company as data from SEQUOIA[29] identified no meaningful differences between arm A and arm B of Cohort 1; however, no EQ-5D data was collected for the "high-risk" population of Cohort 2 (arm C). The HSUVs obtained from SEQUOIA[29] were considered by the company to lack face validity as they were higher than the HSUVs from the UK general population. The company used previously accepted HSUVs from NICE TA689[64] for the PF and PD health states. The EAG has expressed concerns with the evidence reported in Holzner *et al*., (2004)[82] which informs the utilities at PD in NICE TA689.[64]

Under the CMA approach, differences across the total costs of the intervention arms were driven primarily by the acquisition costs of zanubrutinib, acalabrutinib, and ibrutinib. The BNF was the best available source for the list prices and dosing regimens included in the CS base-case. As the first-line treatments were based on BTKi drugs, treatments were given until disease progression, leading to a second-line VenR based treatment or death. All costs were presented in GBP (£), and a 2020/21 price-year was used.

A one-time monitoring cost for VenR at treatment initiation was also accounted for, this cost was associated with laboratory TSL prophylaxis and was extracted from NICE TA561.[3] The costs of AEs were also modelled to have an impact on incremental costs in the company base-case. Cost values were sourced from NHS tariffs [86] but, as mentioned above, their impact on the results was minimal.

Additional costs and resources used related to the PF and PD health state were sourced from NICE TA689[64]. Terminal care costs were applied as a one-off cost when patients transitioned to the death state, cost values were obtained from a single study which did not include CLL patients, hence the EAG questioned its applicability.[87] Health state related resource use and costs were applied equally across treatment arms so that the determinants of costs using CMA approach were the treatments and treatment-related AEs in the CS base-case.

The company's base-case results show that zanubrutinib was associated with cost savings of [redacted] compared with acalabrutinib for the overall untreated CLL population. Similarly, zanubrutinib was associated with cost savings of [redacted] versus ibrutinib.

Probabilistic results following 1000 simulations show similar estimates of cost-savings for zanubrutinib compared with acalabrutinib: [redacted] with a [redacted] probability of being cost-effective at the £20,000 per QALY threshold, and a [redacted] probability of being cost-effective at the £30,000 threshold; and against ibrutinib: [redacted] with a [redacted] probability of being cost-effective at the £20,000 per QALY threshold, and a [redacted] probability of being cost-effective at the £30,000 threshold.

The scenario analysis conducted by the company showed that using subgroup specific data for "high-risk" patients to model survival had a large impact in increasing cost-savings associated with zanubrutinib in both comparisons. Decreasing the discount rate also had the impact of increasing the cost-savings associated with zanubrutinib. While parametric survival distributions with more pessimistic predictions (i.e. higher risks of death or disease progression than the alternative models) reduced cost-savings. Results from the DSA further illustrated that the cost savings associated with zanubrutinib were sensitive to changes in the TTP survival curve. However, in all analyses reported in the CS zanubrutinib remained less costly when compared with acalabrutinib and ibrutinib.

The company presented CMA and CUA results for zanubrutinib compared with acalabrutinib using Cohort 1 data of SEQUOIA[29] to mirror the "unfit" population. This resulted in cost savings of [redacted] and zanubrutinib dominating acalabrutinib. The company also presented CUAs for zanubrutinib versus acalabrutinib and ibrutinib using data from Cohort 2 to mirror the "high-risk" population, in both of these analyses zanubrutinib dominated acalabrutinib and ibrutinib, as it was less costly and more effective, in terms of QALYs gained.

The EAG proposed undertaking a CUA using the company model, as the EAG had concerns about the assumption of non-inferiority. Relative effectiveness data from both OS and PFS in the untreated CLL model was applied. In the EAG base-case zanubrutinib dominated acalabrutinib (incremental costs of [redacted]; incremental QALYs of [redacted]; with [redacted] probability of being cost-effective) and ibrutinib (incremental costs of [redacted]; incremental QALYs of [redacted]; with [redacted] probability of being cost-effective) for the overall untreated CLL population.

Scenarios with worse relative effectiveness versus acalabrutinib, higher utility values assigned to the PD health state, and less optimistic models of TTP and PFS decreased the differences in costs and QALYs gained by zanubrutinib. Zanubrutinib was less costly and less effective when compared with acalabrutinib but is still likely to be considered cost-effectiveness due to the high ICER associated with acalabrutinib vs zanubrutinib when 1) using Model 2 estimates from the MAIC in the untreated population (acalabrutinib ICER = £13,350,239); 2) when health state utilities from SEQUOIA[29] (acalabrutinib ICER = £28,634,340; 3) when using PD disutilities from SEQUOIA[29] (acalabrutinib ICER = £31,266,742); and 4) when data from arm A in Cohort 1 of SEQUOIA[29] was used to mirror the untreated "unfit" population using MAIC data from ELEVATE-TN (acalabrutinib ICER = £15,387,982), and ASCEND (acalabrutinib ICER = £2,788,793). DSA results showed that deterministic results were sensitive changes in the HR estimate for TTP, the HR estimate for PrePS, the drug cost of acalabrutinib relative to zanubrutinib and the drug cost of ibrutinib relative to zanubrutinib.

While the EAG base-case and scenario analyses were robust to changes in assumptions there are important caveats associated with the CUA approach that the EAG must acknowledge. Regarding the relative effectiveness of zanubrutinib versus acalabrutinib or ibrutinib, the EAG base-case assumed a constant hazards approach over the lifetime of the population. This also meant that the effects of the intervention were maintained throughout the duration of the intervention, which could be a lifetime duration as BTKis are administered until disease progression or intolerance. Hence treatment

discontinuation could not be applied to all arms due to lack of data. The model also implied there were no differences in treatment discontinuation across comparator arms.

Moreover, results from the EAG scenario analyses demonstrated that the cost-effectiveness results were highly sensitive to changes in assumptions on TTP, but patient data for TTP were not available for acalabrutinib or ibrutinib. The evidence informing progression in acalabrutinib was derived from a MAIC where it was not possible to differentiate the data across the "unfit" and "high-risk" subgroups. Disease progression in ibrutinib was informed by evidence from R/R CLL patients, which the company assumed were a suitable proxy for untreated "high-risk" CLL patients. However, only 23% of ALPINE participants could be categorised as "high-risk" (i.e., presence of del17p or TP53 mutation).

The time period captured in the follow up from SEQUOIA, with a median follow up of 25.1 months in Cohort 1 treated with zanubrutinib, and 27.7 months in zanubrutinib Cohort 2, was considered too short relative to the 30-year time horizon assumed in the model. Only more mature and longer-term data can reduce these uncertainties, especially if data are produced to facilitate head-to-head comparison between zanubrutinib, acalabrutinib, and ibrutinib in their respective target populations, overcoming any confounders missed in the MAIC.

There are further uncertainties that could not be parametrised within the model, but have been highlighted as key issues, with direct implications to the cost-effectiveness results. These include the comprehensiveness of the searches, the use of an untreated "fit" CLL population from SEQUOIA to model an "unfit" CLL population, and the lack of data on HRQoL for "high-risk" patients.

6.3 Exploratory and sensitivity analyses undertaken by the EAG in the R/R CLL population

This section describes the EAG base-case and scenario analyses conducted on both the EAG and the company base-case analyses. The EAG base-case and scenario analyses use the company's economic model on the R/R CLL population and adopts alternative assumptions.

6.3.1 EAG base-case

Table 6.10 summarises the key issues related to the cost effectiveness, categorised according to the sources of uncertainty categorised as: Transparency; Methods; Imprecision; Bias and indirectness; or Unavailability (as defined by Grimm *et al*., 2020[92]) see Section 6.2.1 for more details.

Table 6.10 lists suggested alternative approaches, expected effects on the cost-effectiveness and whether it is reflected in the EAG base-case, as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections for the R/R population. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories: Fixing errors; Fixing violations; or Matters of judgment (derived from Kaltenthaler 2016[93]) see Section 6.1.1 for more details.

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.10 shows how individual adjustments impact the results, plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case.

No errors were found in the R/R CLL economic model file. However, the EAG consider the assumption on non-inferiority to be unjustified in the comparison of zanubrutinib with acalabrutinib and hence consider the CMA approach adopted by the company to be a violation of accepted best practice.[41] The EAG consider the CMA approach adopted for the comparison of zanubrutinib with ibrutinib in the R/R population to be a conservative assumption. The EAG base-case and scenario analyses were undertaken to assess the impact of alternative assumptions on the cost-effectiveness results using a CUA approach.

The EAG also consider the exclusion of VenR as a comparator in the R/R model to be a deviation from the NICE scope. However, due to the uncertainty in the effectiveness estimates derived by the EAG to enable this comparison (see Section 3.5) the EAG have not addressed this violation in the EAG analyses.

6.3.1.1 Fixing errors

No errors were identified by the EAG.

6.3.1.2 Fixing violations

Description: The company used a CMA approach to model the decision problem, over a CUA in their base-case (see Sections 3.3.4, 3.4 and 4.4.6.2).

How this was addressed by the EAG: As the submitted model for the R/R CLL population followed a partitioned survival approach, the key parameters were OS and PFS, which were used to derive the proportion of progressed patients. The approach the EAG has chosen to model its base-case follows the approach presented by the company in Scenario 15 of the Scenario analysis results that transforms the model into a CUA.

This approach applied the relative effectiveness estimates from the MAIC results of Model 2 comparing ALPINE and ASCEND on the OS and the PFS curves of zanubrutinib from ALPINE[88] to derive the OS and PFS for acalabrutinib. The EAG acknowledge that the choice of MAIC ASCEND Model 2 was the least favourable option for zanubrutinib, The OS and PFS curves for ibrutinib were derived from the ALPINE trial[88] directly. A caveat of this approach was that the method to derive the survival curves for acalabrutinib assumed a constant relative hazard over-time. Moreover, the effect of the treatments was assumed to last for as long as patients stay in the PF state.

6.3.1.3 Matters of judgement

An overview of the key issues related to the cost-effectiveness is presented in Table 6.10

Table 6.10: Overview of key issues related to the cost-effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Use of a CMA as the company's base-case	3.4/4.3.6.2/ 4.4.6.2	Transparency; Imprecision	A CUA using HR estimates from different MAIC models	+/-	Explored as the EAG base-case	Better quality evidence/data for the relative efficacy between zanubrutinib and acalabrutinib
Uncertainty in the utility estimates used in the company's economic model	4.3.8/4.4.8	Transparency	Utility data derived from the ALPINE trial[30]	+	Explored in scenario analyses 1-2	No
Immaturity in the trial data and parametric survival functions	4.3.6.1/4.4. 6.1	Imprecision; Unavailability	Alternative distribution functions used to model PFS and OS	+	Explored in scenario analyses 4-7	ALPINE data from cut-off dates beyond December 2021 could diminish some of the uncertainty. Longer term data is lacking in this population, which could better inform the selection of parametric models

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator;
[b] Explored.
Abbreviations: CMA = Cost minimisation analysis; CUA = Cost utility analysis; EAG = External Assessment Group; ICER = Incremental cost effectiveness ratio; MAIC = Matching-adjusted indirect comparison; OS = Overall Survival.

1. Uncertainty in the utility estimates used in the company's economic model (Sections 4.3.8 and 4.4.8)

The CUA that was presented by the company as a scenario analysis (see Section 5.1.3) utilised previously approved utility values from NICE TA689[64] for the PF and PD health states, as utilities obtained from ALPINE[88] showed higher values than the average UK population.[6] PF and PD health state utility values from the CS base-case were maintained in the EAG base-case; however, the EAG undertook a scenario analysis using utility values from ALPINE.[88]

The EAG was had concerns about the source used to derive the utility value for the PD state (see Section 4.3.8.2); therefore, a scenario explored by the EAG used the difference in mean utility values between PF and PD obtained from ALPINE[88] as a PD disutility and applied this disutility value to the PF utility value in the CS base-case to derive an alternative utility value for the PD health state only.

2. Immaturity in the trial data and parametric survival functions (Section 4.4.6.1)

The CS base-case selected a Weibull distribution to extrapolate PFS and OS over the long-term. The clinical advice sought by the EAG suggested the Weibull predictions for PFS might present a pessimistic scenario relative to clinical practice. The scenario analysis presented by the company explored the Gompertz distribution as an alternative to model PFS and the Exponential distribution as an alternative to model OS.

The EAG maintained the Weibull distribution for PFS in its base-case but explored the impact of distributions with more optimistic and pessimistic predictions around its base-case model. The Weibull distribution is also kept for OS; however, as this presents the most pessimistic predictions relative to the other distributions, scenarios are explored using less pessimistic distributions on the EAG base-case model.

6.3.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case. A list of scenarios is presented in Table 6.13, results are presented in Table 6.14 and Table 6.15.

6.3.2.1 List of exploratory scenario analyses

This section describes the scenario and sensitivity analyses conducted by the EAG. The EAG conducted nine scenario analyses not conducted by the company. All these scenario and sensitivity analyses are described below.

1. Utility estimates from ALPINE (Section 4.4.8)

The EAG used utilities obtained from the ALPINE trial[88] for PF and PD health states to explore an alternative scenario from the values used in the company base-case. The EAG does not reject the values used in the company base-case, therefore health state utilities remain unchanged in the EAG base-case; however, the EAG considers it relevant still to represent the uncertainty around these estimates by exploring this alternative scenario.

2. Alternative utilities for PD health state (Section 4.4.8)

The EAG explored the impact of varying the utilities for patients in the PD health state. The EAG estimated a progression disutility as the difference between the PF and PD health state utilities derived from the ALPINE trial.[88] This derived disutility was applied to the base-case PF utility value to generate the alternative utility value for the PD health state.

3. Equivalent adverse events profile across all arms (Section 4.4.7)

To explore the impact of the different AE incidences across comparator arms, the incidence rates from the zanubrutinib arm in the ALPINE trial[88] were applied across the comparator arms in the model.

4. Optimistic PFS – Log-normal distribution (Section 4.4.6.1.1)

The EAG considers the PFS predictions generated from the Weibull model to potentially present a pessimistic scenario. A log-normal distribution was used as an alternative to model PFS over the long-term, which presents a scenario with a lower risk for progression.

5. Pessimistic PFS – Gompertz distribution (Section 4.4.6.1.1)

The Gompertz distribution presented a more pessimistic PFS outlook than the Weibull. Although this is likely to be an extreme scenario, this will serve as a test of the robustness of the results under alternative PFS assumptions.

6. Optimistic OS – Log-normal distribution (Section 4.4.6.1.2)

The Weibull distribution applied to the OS data from R/R CLL patients presents the most pessimistic predictions of survival over the long-term. A scenario analysis using the Log-normal distribution explored the impact of an optimistic OS scenario relative to the alternative parametric distributions presented.

7. Less optimistic OS – Exponential distribution (Section 4.4.6.1.2)

The Exponential distribution was chosen by the EAG as a midpoint between the Weibull distribution used in the base-case and the optimistic scenario which used the Log-normal distribution.

8. Idelalisib combination delivered to 5% of patients (Section 4.4.9)

The CS base-case assumed that, following disease progression, R/R CLL patients moved to a second line therapy where 80% of patients received VenR, while the remaining 20% received an idelalisib-rituximab combination. It was noted by the clinical expert consulted by the EAG that idelalisib is rarely used in clinical practice in the UK, hence this scenario explores the impact of reducing the proportion of patients treated with idelalisib-rituximab to 5%.

9. A time horizon of 15 years (Section 5.2.1)

The EAG considers the 30-year lifetime horizon of the CS base-case to be appropriate to represent the decision problem. However, a shorter time horizon was used to explore the medium-term estimates of cost-effectives for zanubrutinib.

6.3.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.3.3.1 The EAG base-case and scenario analyses

In section 6.2.1, the features of the EAG base-case were presented, which was based on various changes compared to the company base-case relating to both fixing of errors and matters of judgement (MJ). The impact of these are shown in Tables 6.11 and 6.12 for the comparisons of zanubrutinib versus acalabrutinib and zanubrutinib versus ibrutinib respectively.

Table 6.11: Deterministic and probabilistic EAG base-case results – zanubrutinib versus acalabrutinib

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case (CMA) – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	
Acalabrutinib	[redacted]	[redacted]			
CS base-case (CMA) – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	
Acalabrutinib	[redacted]	[redacted]			
EAG base-case (CUA) – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£340,019*
Acalabrutinib	[redacted]	[redacted]			
EAG base-case (CUA) – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£342,991*
Acalabrutinib	[redacted]	[redacted]			

*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib

Abbreviations: CMA = Cost-minimisation analysis; CS = Company submission; CUA = Cost-utility analysis; EAG = External Assessment Group; ICER = Incremental cost-effectiveness ratios; QALYs = Quality-adjusted life years.

Table 6.12: Deterministic and probabilistic EAG base-case results – zanubrutinib versus ibrutinib

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case (CMA) – Deterministic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]			
CS base-case (CMA) – Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]			
EAG base-case (CUA) – Deterministic					

Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
EAG base-case (CUA) - Probabilistic					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]			
Abbreviations: CMA = Cost-minimisation analysis; CS = Company submission; CUA = Cost-utility analysis; EAG = External Assessment Group; ICER = Incremental cost-effectiveness ratios; QALYs = Quality-adjusted life years.					

Table 6.13 summarises the EAG scenario analyses that are set out in Section 6.3.2.1.

Table 6.13: List of EAG scenario analyses in the R/R CLL model

Scenario	Scenario description
1	Utility estimates from ALPINE[88] (Section 4.4.8): ALPINE derived utilities [redacted]
2	Alternative utilities for PD health state (Section 4.4.8): ALPINE derived disutility at the PD health state = [redacted]
3	Equivalent adverse events profile across all arms (Section 4.4.7)
4	Optimistic PFS – Log-normal distribution (Section 4.4.6.1.1): Lower risk of progression relative to the base-case
5	Pessimistic PFS – Gompertz distribution (Section 4.4.6.1.1): Higher risk of progression relative to the base-case
6	Optimistic OS – Log-normal distribution (Section 4.4.6.1.2): Lower risk of mortality relative to the base-case
7	Less optimistic OS – Exponential distribution (Section 4.4.6.1.2): Moderately lower risk of mortality relative to the base-case
8	Idelalisib combination delivered to 5% of patients (Section 4.4.9): Proportion of patients receiving idelalsib-rituximab reduced from 20% to 5%
9	A shorter time-horizon (15 years) (Section 5.2.1)
Abbreviations: CLL = Chronic lymphocytic leukaemia; EAG = External Assessment Group; OS = Overall survival; PFS = Progression-free survival; R/R = Relapsed or refractory.	

The deterministic results of these EAG scenario analysis set out in Table 6.13 are summarised in the Tables below. Table 6.14 report the results for zanubrutinib versus acalabrutinib and Table 6.15 reports the results for zanubrutinib versus ibrutinib.

Table 6.14: Deterministic results of EAG scenario analyses (zanubrutinib versus acalabrutinib)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	NA	[redacted]	[redacted]	£340,019 *

Scenario 1	EAG base-case utilities: PF = 0.748; PD = 0.600	ALPINE derived utilities [redacted]	[redacted]	[redacted]	£253,248 *
Scenario 2	EAG base-case PD utility = 0.600	ALPINE derived PD utility = [redacted]	[redacted]	[redacted]	£287,909 *
Scenario 3	AE incidence from ASCEND	AE incidence from the zanubrutinib arm in ALPINE	[redacted]	[redacted]	£339,746 *
Scenario 4	Weibull distribution for PFS	Log-normal distribution for PFS	[redacted]	[redacted]	£544,432 *
Scenario 5	Weibull distribution for PFS	Gompertz distribution for PFS	[redacted]	[redacted]	£256,673 *
Scenario 6	Weibull distribution for OS	Log-normal distribution for OS	[redacted]	[redacted]	£544,171 *
Scenario 7	Weibull distribution for OS	Exponential distribution for OS	[redacted]	[redacted]	£378,728 *
Scenario 8	Idelalisib 20%	Idelalisib 5%	[redacted]	[redacted]	£341,352 *
Scenario 9	30-year lifetime horizon	15-year time horizon	[redacted]	[redacted]	£510,660 *

*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib

Abbreviations: AEs = Adverse events; EAG = External Assessment Group; ICER = Incremental cost-effectiveness ratio; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PFS = Progression-free survival; QALYs = Quality-adjusted life years.

Table 6.15: Deterministic results of EAG scenario analyses (zanubrutinib versus ibrutinib)

Scenario	EAG base-case input	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER(£/QALY)
	EAG base-case	NA	[redacted]	[redacted]	Zanubrutinib dominant

Scenario 1	EAG base-case utilities: PF = 0.748; PD = 0.600	ALPINE derived utilities [redacted]	[redacted]	[redacted]	£12,351,199 *
Scenario 2	EAG base-case PD utility = 0.600	ALPINE derived PD utility = [redacted]	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 3	AE incidence from the ibrutinib arm in ALPINE	AE incidence from the zanubrutinib arm in ALPINE	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 4	Weibull distribution for PFS	Log-normal distribution for PFS	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 5	Weibull distribution for PFS	Gompertz distribution for PFS	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 6	Weibull distribution for OS	Log-normal distribution for OS	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 7	Weibull distribution for OS	Exponential distribution for OS	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 8	Idelalsib 20%	Idelalsib 5%	[redacted]	[redacted]	Zanubrutinib dominant
Scenario 9	30-year lifetime horizon	15-year time horizon	[redacted]	[redacted]	Zanubrutinib dominant

Abbreviations: AEs = Adverse events; EAG = External Assessment Group; ICER = Incremental cost-effectiveness ratio; OS = Overall survival; PD = Progressed disease; PF = Progression-free; PFS = Progression-free survival; QALYs = Quality-adjusted life years.

6.3.4 EAG base-case results for the R/R CLL population

The EAG analysis shows that zanubrutinib is less costly and less effective than acalabrutinib (Table 6.11), however it dominates ibrutinib (Table 6.12). Figure 6.7 illustrates that for all 1,000 iterations of

the PSA, zanubrutinib was less costly than both acalabruitin and ibrutinib. In the EAG base-case, zanubrutinib compared with acalabrutinib had a [redacted] probability of being considered cost-effective at a £20,000 threshold for an additional QALY (Figure 6.8). Zanubrutinib dominated ibrutinib and the probability of zanubrutinib being considered cost-effective was [redacted] at a £20,000 threshold for an additional QALY (Figure 6.8).

The scenarios which had the biggest impact on the EAG base-case were:

- Using utility estimates from ALPINE trial (Scenario1) for zanubrutinib versus ibrutinib
- Using Log-normal distribution for PFS (Scenario 4)
- Using Gompertz distribution for PFS (Scenario 5)
- Using Exponential distribution for OS (Scenario 7) for zanubrutinib versus ibrutinib
- Using shorter time horizon (Scenario 9)

Figure 6.7: Cost-effectiveness plane for zanubrutinib versus ibrutinib and acalabrutinib

Abbreviations: QALYs = Quality-adjusted life years.

Figure 6.8: Cost-effectiveness acceptability curves for zanubrutinib versus ibrutinib and acalabrutinib

Results from the DSA conducted on the EAG base-case show that the parameters that had the largest impact on costs (Figure 6.8 and Figure 6.10) were:

- Hazard ratio for PFS (zanubrutinib vs acalabrutinib)
- Weibull model to project PFS for zanubrutinib (zanubrutinib vs acalabrutinib)
- Weibull model to project PFS for ibrutinib (zanubrutinib vs ibrutinib)

The parameters that had the largest impact on QALYs from the DSA on the EAG base-case (Figure 6.9 and Figure 6.11) were:

- Weibull model to project OS for zanubrutinib (zanubrutinib vs ibrutinib)
- Hazard ratio for OS (zanubrutinib vs acalabrutinib)
- Hazard ratio for PFS (zanubrutinib vs acalabrutinib)

The cost difference remained negative between zanubrutinib and the comparator arms across the DSA results (Figure 6.9 and Figure 6.11). In the acalabrutinib arm, all the incremental QALYs remained negative across the DSA results, except for the HR estimates for OS (Figure 6.10). However, the incremental QALYs changed from negative to positive in most of the DSA results in the ibrutinib arm (Figure 6.12).

Figure 6.9: Tornado plot: Incremental costs zanubrutinib versus acalabrutinib

Abbreviations: AE = Adverse events; OS = Overall survival; PFS = Progression-free survival; TLS = Tumour lysis syndrome.

Figure 6.10: Tornado plot: Incremental QALYs zanubrutinib versus acalabrutinib

Abbreviations: AE = Adverse event; BSA = Body surface area; kg = Kilogram; m = Metre; OS = Overall survival; PFS = Progression-free survival; QALYs = Quality-adjusted life years.

Figure 6.11: Tornado plot: Incremental costs zanubrutinib versus ibrutinib

Abbreviations: AE = Adverse events; OS = Overall survival; PFS = Progression-free survival; TLS = Tumour lysis syndrome.

Figure 6.12: Tornado plot: Incremental QALYs zanubrutinib versus ibrutinib

Abbreviations: AE = Adverse event; BSA = Body surface area; kg = Kilogram; m = Metre; OS = Overall survival; PFS = Progression-free survival; QALYs = Quality-adjusted life years.

6.3.5 Conclusions of the cost-effectiveness section for the R/R model

A summary of the company SLR to inform the cost-effectiveness analyses is provided in Section 6.2.6.

The EAG consider that the company mostly complied with the NICE reference however, the EAG have two concerns; 1) the company's justification for using a CMA in the base-case analysis to compare zanubrutinib with acalabrutinib and 2) the exclusion of VenR as a comparator in the economic model.

The assumption of non-inferiority was not satisfied for this comparison based on the multiple MAIC analyses where no statistically significant difference was found in the clinical outcomes. Hence, the EAG do not consider the CMA approach adopted by the company to be the most appropriated method to represent the decision problem. The EAG however acknowledge that in the comparison between zanubrutinib with ibrutinib the adoption of a CMA was a conservative assumption by the company. The company did adopt a CUA approach as a scenario analysis for both pairwise comparisons across six scenario analyses. The EAG adopted this CUA approach to compare zanubrutinib with acalabrutinib and ibrutinib in R/R CLL as the EAG considered this to be the most appropriate approach to address the decision problem.

To model the R/R CLL population the company used a partitioned survival model. The three mutually exclusive health states were PF, PD and dead (the absorbing state). All patients started in PF, which was defined using the PFS for each treatment and constrained by OS. Patients could remain in PF or move to either PD or dead. The model adopted a lifetime horizon, 30 years. Although the EAG felt further justification for the model choice could have been provided by the company overall the EAG had no concerns with the model structure.

The R/R CLL population was designed to represent adult patients who had at least one previous systemic therapy. Data on the baseline characteristics of these patients was mostly provided from the ALPINE trial, which was a direct head-to-head comparison of zanubrutinib and ibrutinib. The interventions being compared were the same as those being evaluated in the untreated CLL economic model (see Section 6.2.6) for details on dosage. The EAG consider the population and BTKi interventions to be appropriate however, it considers the company has deviated from the decision problem by excluding VenR as a comparator in this model. Based on BSH guidelines and clinical advice to the EAG, the EAG disagree with the company's rationale for excluding VenR. The EAG undertook additional analyses to estimate the effectiveness of zanubrutinib compared to VenR [PFS HR = 1.48 (95% CI 0.49, 4.45); and OS HR = 1.87 (95% CI 0.61, 5.79)]. Based on the point estimates, VenR is more effective than zanubrutinib but, given the wide confidence intervals, the EAG did not want to incorporate this uncertainty into the cost-effectiveness analyses and consider that ideally the search and inclusion criteria for their SLR should be revised to ensure all relevant effectiveness data associated with VenR is identified. These data should then be incorporated into the R/R CLL model.

The Weibull distribution was chosen by the company to extrapolate both PFS and OS for zanubrutinib. The choice of this model was the most pessimistic, but it reflected the trial data available at the time. The EAG have concerns over the process used by the company to select their survival functions especially given the lack of longer-term data to compare the extrapolations to. However, as the company chose the most conservative distribution for their base-case the EAG are satisfied with this and explored less conservative assumptions in the EAG scenario analyses.

Similar to the untreated CLL economic model the R/R CLL economic model accounted for ≥ grade 3 treatment related AEs but they had to occur in ≥ 2% of the patient population. The application of AEs

was similar to that of the untreated CLL economic model in that they occurred for the first cycle only (see Section 6.2.6).

Similar to the utility data derived from SEQUOIA, the utility data from ALPINE was also considered by the company to lack face validity as the HSUV for PF and PD were higher than the age-sex matched general population HSUVs for the UK. The company did not undertake any scenario analyses exploring the uncertainty in these results. The EAG have no further comments on HSUVs, only those that were previously raised (Section 6.2.6).

Costs associated with the BTKi treatments, healthcare resource use and terminal care were the same as those applied in the untreated model (see Section 6.2.6). For patients who progressed to PF it was assumed that they would be treated with either VenR or idelalisib-rituximab, however the EAG had concerns about the proportion of patients receiving idelalisib-rituximab based on clinical advice. This assumption was explored by the EAG in a scenario analysis.

The company's base-case results, which assumed life years gained and QALYs were equivalent between treatments, show that zanubrutinib was less costly than both ibrutinib ([redacted]) and acalabrutinib ([redacted]).

The company's PSA, using 1,000 iterations, have similar conclusions in that zanubrutinib was still the preferred treatment as it was associated with cost-savings compared to ibrutinib ([redacted]) and acalabrutinib and ([redacted]).

The company undertook a number of scenario analyses to explore potential uncertainty in their base-case results. The scenarios that reduced the cost savings associated with zanubrutinib were:

- assuming a higher discount rate;
- using data from an earlier data cut from ALPINE;
- using IRC-assessed PFS;
- changing the survival curve for PFS to a Gompertz distribution; and
- using TTTD from ALPINE in the comparison between zanubrutinib and ibrutinib.

In all of these analyses zanubrutinib remained the preferred treatment option due to the cost-savings associated with it compared with acalabrutinib and ibrutinib. However, when a CUA scenario analysis was adopted the cost-savings associated with zanubrutinib were reduced. When compared with ibrutinib, zanubrutinib was dominant as it was less costly and provided more QALYs. When compared with acalabrutinib, for some of the CUA scenario analyses, zanubrutinib was less costly and less effective in terms of QALYs gained compared with acalabrutinib. However, zanubrutinib was still the preferred treatment option due to the high ICER associated with acalabrutinib.

The EAG base-case adopted a CUA approach but maintained the assumptions in the company's base-case and used the company's preferred utility values. In the comparison with acalabrutinib, zanubrutinib was less costly ([redacted]) and less effective ([redacted] QALYs), however zanubrutinib was still the preferred treatment option as the more costly and effective acalabrutinib, had an ICER of £340,019 compared with zanubrutinib. This was the same conclusion found in the PSA of the EAG base-case, zanubrutinib was less costly ([redacted]) and less effective ([redacted] QALYs) but acalabrutinib compared with zanubrutinib had an ICER of £342,991. When compared with ibrutinib, as expected based on the results of the ALPINE trial, zanubrutinib was dominant as it was less costly and more effective in both the deterministic ([redacted], [redacted] QALYs) and probabilistic analyses ([redacted], [redacted] QALYS). For

both pairwise comparisons zanubrutinib had [redacted] probability of being considered cost-effective at £20,000 and £30,000 thresholds for an additional QALY.

The EAG undertook a number of scenario analyses to address uncertainty in the EAG base-case assumptions. While there were variations in the point estimates overall the conclusions remained the same in that zanubrutinib was less costly and less effective than acalabrutinib but still the preferred treatment option due to the ICER associated with acalabrutinib and zanubrutinib dominated ibrutinib in all but one analysis, but it would still be considered the preferred treatment option.

While the EAG base-case and scenario analyses were robust to changes in assumptions there are important caveats associated with the CUA approach that the EAG must acknowledge. The PFS and OS curves for zanubrutinib and ibrutinib were jointly modelled using ibrutinib as the reference arm from ALPINE data.[88] The PFS and OS curves for acalabrutinib were derived applying the hazard ratios from the Model 2 MAIC results using ASCEND data.[35] This approach assumed constant relative hazards between zanubrutinib and acalabrutinib over the lifetime horizon of the model. Results from the scenario analysis between zanubrutinib and ibrutinib show that effectiveness results were sensitive to changes in assumptions of relative effectiveness compared to the constant proportional hazards assumption.

This approach also assumed that the effects of the intervention and comparators were maintained for the duration of each treatment, which could have a lifetime duration, as treatment discontinuation could not be applied to all arms due to lack of data. The model also implied there were no differences in treatment discontinuation across comparator arms.

Moreover, results from the scenario analyses demonstrated that cost-effectiveness results were highly sensitive to assumptions around PFS and OS. The evidence informing progression in acalabrutinib was derived from the MAIC against ASCEND[35], which presented wide confidence intervals and different point estimates of relative effectiveness compared with the MAIC against ELEVATE-RR.[36] Only more mature and longer-term data can reduce these uncertainties, especially if data are produced making a head-to-head comparison between zanubrutinib and acalabrutinib, overcoming any confounders missed in the MAIC. Moreover, data on time to progression alone would allow for more sophisticated modelling structures, such as a Markov approach, to produce more accurate results. Finally, there are further uncertainties that could not be parametrised within the model but have been highlighted as key issues and are summarised in Section 6.2.6. An additional issue with the R/R CLL economic model is the exclusion of VenR as a comparator.

7 References

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Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 30 March 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL (EAG issue 1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, Page 43: "Clinical advice to the EAG also disagreed with the exclusion of venetoclax with rituximab (VenR). They disagreed with the company's perspective that VenR, or venetoclax monotherapy, would not be recommended in patients who have not previously received treatment with a Bruton tyrosine kinase inhibitor (BTKi), as there will be some patients who have had CIT for whom a BTKi would be a second-line option."	The Company requests the text to be amended to: "Clinical advice to the EAG also disagreed with the exclusion of venetoclax with rituximab (VenR). They disagreed with the company's perspective that VenR~~, or venetoclax monotherapy,~~ would not be recommended in patients who have not previously received treatment with a Bruton tyrosine kinase inhibitor (BTKi), as there will be some patients who have had CIT for whom a BTKi would be a second-line option. **However, the EAG acknowledge that this would only**	**<u>VenR for patients with R/R CLL</u>** The Company acknowledges that a relatively small proportion of patients in the R/R setting may receive treatment with VenR. However, UK prescribing data for a sample of [redacted] with CLL, collected by [redacted] in December 2022, reported that only [redacted] of patients received second-line treatment with VenR whereas [redacted] of patients receive second-line treatment with a BTKi. As such, BTKis represent the main-stay treatment option for patients in the R/R setting and particularly in those who have only received one prior line of treatment. This is likely due to VenR being a more intensive dosing regimen and the associated risk of tumour lysis syndrome. In comparison, [redacted] of patients receive third-line treatment with a venetoclax-based therapy whereas only [redacted]% of patients receive third-line treatment with a BTKi. This suggests that the treatment sequencing algorithm in patients not treated with a BTKi in first line is to receive a BTKi in second-line and a BCL2i in third-line. **<u>Venetoclax monotherapy</u>**	The EAG have not commented on VenR for patients with R/R CLL except as a matter of judgement. The EAG cannot comment on the IQVIA data as they do not have access to details of the data request nor data the in individual or summary form. However, based on the company's quantitative survey data provided to the EAG by the company in their response to the clarification letter,[1] the clinicians surveyed reporting treating [redacted] of R/R CLL patients with VenR, which the EAG does not consider to be a small proportion of patients given that [redacted] were treated with a BTKi. In addition, [redacted] Regardless, of which data is used the EAG considers that a significant minority of patients receive VenR as a second line therapy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	represent a small proportion of patients"	The Company would like to highlight that venetoclax monotherapy is recommended within its marketing authorisation for treating CLL in adults:[1] • With a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or, • without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor. As such, patients without a 17p deletion or TP53 mutation would need to be double refractory to CIT and a B-cell receptor pathway inhibitor prior to receiving venetoclax monotherapy. Alternatively, patients with a 17p deletion or TP53 mutation who have progressed disease after treatment with a B-cell receptor pathway inhibitor would likely have been treated with a BTKi, as opposed to a PI3K inhibitor such as idelalisib, which is rarely used in clinical practice following the introduction of BTKi and BCL2i therapies. Therefore, venetoclax monotherapy is	With regards to venetoclax monotherapy, the EAG have removed this from the statement as suggested by the company. Section 2.3 (p.43) has been updated with the following text: "They disagreed with the company's perspective that VenR, would not be recommended in patients who have not previously received treatment with a Bruton tyrosine kinase inhibitor (BTKi), as there will be some patients who have had CIT for whom a BTKi would be a second-line option."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		not a relevant comparator to zanubrutinib in the populations of interest.	
Section 2.3, Page 43: "The EAG's clinical advisor agreed that VenO would be an option for untreated CLL and disagreed with the company's statement that usage was low in the UK."	The Company requests the text to be amended to: "The EAG's clinical advisor agreed that VenO would be an option for untreated CLL and disagreed with the **UK prescribing data collected by IQVIA and UK clinical expert opinion received by the company which highlighted** that usage was low in the UK."	Whilst the EAG clinical advisor disagreed with the Company's statement that usage was low in the UK, it should be highlighted that the Company's statement was data driven and supported by multiple clinical experts. **<u>IQVIA prescribing data</u>** UK prescribing data for a sample of [redacted] with CLL collected by IQVIA in December 2022, reported that in previously untreated patients who are considered "unfit" (defined as patients aged >65 or patient age ≤65 with comorbidities), [redacted] are treated with BTKis. In contrast, only [redacted] of "unfit" patients receive treatment with VenO.[2] Furthermore, [redacted] of previously untreated patients with a 17p deletion or TP53 mutation were treated with a BTKi compared to only [redacted] of patients receiving treatment with VenO.[2] **<u>UK clinical expert opinion</u>** The low usage of VenO was supported by feedback received from two clinical experts at an advisory board (03 November 2022) conducted	Thank you for highlighting. The EAG have updated the EAG comment to state that the clinical advice was against what was included in the CS. Section 2.3 (p.43) the following sentence has been included: "The EAG's clinical advisor agreed that VenO would be an option for untreated CLL and disagreed with the CS that usage was low in the UK". This statement is supported by the company's quantitative survey data provided to the EAG by the company in their response to the clarification letter[1] The clinicians surveyed reporting treating [redacted] of "high-risk" untreated CLL patients and [redacted] of not "high risk" "unfit" untreated CLL patients with VenO over the past 12 months which supports that VenO is used in the UK and usage is still a significant minority of patients.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		by the Company who supported the positioning of zanubrutinib as an alternative BTKi treatment option and not as an alternative to VenO. They also noted that the introduction of zanubrutinib would not change the decision of whether to treat with a venetoclax-based regimen or a BTKi in either previously untreated patient population.[3] Furthermore, these findings were supported by an online quantitative survey of 30 UK-based CLL specialists conducted by the Company and by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[4,5] Within the interviews, clinicians confirmed that VenO was typically used to treat "fitter" patients who are younger and do not present with comorbidities given the risk of tumour lysis syndrome and gastrointestinal side effects.[4,5] As such, VenO is typically used within the subgroup of patients for whom FCR or BR therapy is suitable. In contrast, a BTKi would typically be prescribed for previously untreated: - elderly patients or patients with comorbidities that would typically be unsuitable for FCR and BR therapy. - patients with a 17p deletion or TP53 mutation.	The EAG's clinical advisor agreed that a BTKi would be chosen as a first line treatment in the majority of untreated CLL patients with a 17p deletion or TP53 mutation however they noted that the incidence of p53 mutation/deletion in untreated CLL is low. The EAG cannot comment on the IQVIA data as they do not have access to this.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		<u>UK British Society for Haematology (BSH) clinical guidelines</u> Whilst VenO is considered as an option in this population, the 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 regimen (i.e. a venetoclax-based regimen).[6] As such, VenO should not be considered a comparator in this population, with VenO being used in cases when a BTKi is unsuitable.	
Section 3.5, Pages 109 – 113: This section describes two NMA analyses conducted by the EAG to compare zanubrutinib with VenR and with VenO. The Company strongly believes that these analyses lack clinical and statistical validity and are subject to substantial	The Company requests the NMA analyses conducted by the EAG and all related text is removed from the report.	**<u>Use of NMA methodology</u>** The Company would like to highlight the NMA methodology is subject to substantial uncertainty due to the inability to adjust for across trial heterogeneity and requirement for a connected network of evidence. Due to significant heterogeneity in the design and comparators selection in CLL clinical trials, matching-adjusted indirect comparison (MAIC) is deemed a more appropriate methodology in adjusting for cross-trial heterogeneity and avoiding basing comparative estimates on distant connection in a network of evidence, in line with previous technology appraisals in this patient population.[7–9]	The EAG do not agree with the company's interpretation of Section 3.5 of the EAG report. To summarise, the reason for the EAG NMA analyses was to explore the potential consequences of the company excluding comparators from the NICE scope. In addition, the EAG thought it important to identify whether there were plausible opportunities for the company to address this uncertainty. There are several reasons why this exclusion by the company was cause for concern: a) Ven-R is a NICE recommended treatment (hence its inclusion in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
uncertainty. As such, these analyses should not be considered fit for purpose. All subsequent mentions of the NMA analyses should also be removed from the document: - **Section 1.3, Page 17, Table 1.3, Row 4** - **Section 6.3.5, Page 234**		This was supported by the EAG as described in Section 3.3, Page 87 and Section 3.4, Page 108 of the report: - *"The EAG accept concerns raised by the company in the CS regarding significant heterogeneity in the design and selection of comparators in CLL trials and agree that the underlying assumption of an NMA would not be valid. Therefore, the EAG agree it was appropriate to conduct MAICs for the comparators considered in the CS".* - *"The EAG acknowledge that heterogeneity was present and the rationale for conducting MAIC analyses as described in the CS appeared reasonable."* **<u>Issues with the network used to inform the comparison of zanubrutinib with VenR in previously treated patients with CLL</u>** The Company would like to highlight that there are several limitations associated with the network used to connect zanubrutinib with VenR: - **Use of the ASCEND trial to connect acalabrutinib to VenR**: In the ASCEND study, the comparator arm was	the NICE scope) and therefore there is good reason to consider this treatment a potentially valid comparator b) Our clinical advisor also confirmed that it was an important comparator. In the view of the EAG, it was necessary to explore whether this decision by the company potentially led to important uncertainties on the clinical- and cost-effectiveness of zanubrutinib. The purpose of the exploratory analyses and their limitations were very clearly stated in the EAG report (p.110) to avoid this misunderstanding, in addition: "this scoping exercise enabled an initial examination of whether it would have been possible for the company to conduct MAIC analyses between zanubrutinib and VenR." This scoping analyses showed that it would have been feasible for the company to conduct MAIC analyses comparing their treatment with a NICE recommended comparator included in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		investigator's choice between idelalisib-rituximab or bendamustine-rituximab (BR) whereas in MURANO the comparator arm was BR only. Therefore, comparing ASCEND and MURANO through the BR arm will likely not produce reliable results given that the ASCEND control arm will be confounded by idelalisib-rituximab, especially as idelalisib and bendamustine have different mechanisms of action and have not been formally compared prior to pooling within the analyses. - **Lack of reporting on the distribution of effect modifiers between trials included within the network to assess heterogeneity**: No assessment was made to determine whether the studies included within the network were conducted in comparable patient populations, which can lead to confounding of the NMA results. If adjustments were made for heterogeneity through the use of a random effects model, no formal assessment was made on the use of priors.	the NICE scope. Deleting this section would withhold information that may be of potential use to decision-making. The company included in their response several comments on the statistical analyses. The EAG strongly disagrees with these comments and highlights several misunderstandings and factual inaccuracies below: 1) That the EAG did not conduct MAIC analyses. EAG response: the EAG did not have access to individual participant data therefore it was not possible to conduct MAIC analyses. This is clearly stated in the EAG report (p.110) and is recognised in the company's response: "Since the EAG do not have access to IPD for any technologies in this topic area, we could not conduct MAIC analyses." The EAG used the most appropriate methods based on the data available to them and within the time constraints for critiquing the company submission. Our

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		This leads to high uncertainty in the network, as acknowledged by the EAG in Section 3.5.1, Pages 110-111: - *"The structure of the network means any comparison is likely to be highly uncertain."* **<u>Issues with the network used to inform the comparison of zanubrutinib with VenO in previously untreated patients with CLL</u>** The Company would like to highlight that there are several limitations associated with the network used to connect zanubrutinib with VenO: - **Use of ELEVATE-TN trial to connect acalabrutinib to VenO**: In the ELEVATE-TN trial, patients in the chlorambucil-obinutuzumab group were able to cross over to receive acalabrutinib monotherapy if they had IRC-supported disease progression, meaning that the treatment effect in the chlorambucil-obinutuzumab arm was confounded by the treatment effect of acalabrutinib. Whilst no crossover was allowed in CLL14, comparing CLL14 and ELEVATE-TN through chlorambucil-obinutuzumab will likely cause unreliable results.	purpose was to critique the company's submission and to identify potential uncertainties. We think this section serves that purpose. 2) Use of ASCEND trial EAG response: the limitation of using the ASCEND trial is clearly stated in the EAG report (p.110): "the node "Control" is broader than the EAG would prefer, including BR (the comparator in the MURANO trial) and investigators' choice of BR or idelalisib plus rituximab (I-R) (the comparator in the ASCEND trial).[2,3] Although ASCEND found similar outcomes for either of the investigators' choice comparators, uncertainties remain regarding the comparability between comparators included in the MURANO and ASCEND trials." 3) No assessment to determine whether network conducted in comparable patient populations. EAG response:

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		- **Lack of reporting on the distribution of effect modifiers between trials included within the network to assess heterogeneity**: No assessment was made to determine whether the studies included within the network were conducted in comparable patient populations, which can lead to confounding of the NMA results. If adjustments were made for heterogeneity through the use of a random effects model, no formal assessment was made on the use of priors. **<u>Uncertainty in statistical methods used to conduct the NMA</u>** The NMA was not conducted in line with the guidance outlined in the NICE methods guide and lacked key elements to ensure that the results were justifiable and interpretable: - **Lack of feasibility assessment**: A formal assessment of the feasibility of conducting a NMA was not performed and the risk of bias was not assessed. The data sources do not appear to be systematically searched as the data sources used in the NMA seem to be based on the NICE TA561 and TA663	a) There is detailed discussion by the EAG on heterogeneity across the network and distribution of effect modifiers. This is in addition to those assessments reported by the company in their submission which also informed the EAG analyses – therefore this statement by the company is factually incorrect. b) The EAG attempted to minimize potential impact on analyses using a variety of methods including: i) use of the unanchored MAIC estimates (Models 1 and 2) for zanubrutinib versus acalabrutinib reported in the CS (from ASCEND and ALPINE); ii) removed the acalabrutinib versus ibrutinib comparison (from ELEVATE-RR) as these data were a potential threat to the consistency assumption of the NMA.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		and as such, it is uncertain whether the NMA uses the most appropriate data sources and whether the most appropriate trial data cut-offs were used. Furthermore, the analyses did not compare the baseline cohort characteristics between trials, the study design, the treatment doses, outcome definitions or the duration of follow-up. - **Limited reporting on statistical methods used**: It is unclear what statistical methods were used within the NMA and whether Bayesian or frequentist methodology was adopted. Fixed effects models would not be appropriate as they do not adjust for across trial heterogeneity, which the EAG noted in their report that this was an issue across trials in CLL. It is unclear whether the EAG used random effects models. Furthermore, the EAG have not reported any information on the selection of priors. Additionally, no assessments of model convergence were reported. Given the issues with lack of reporting, it is not possible for the Company to assess the appropriateness of the methods used or replicate the results. Overall, the reporting	This is all clearly stated in the EAG report (p.111). 4) No assessment of priors or inconsistency between direct and indirect evidence EAG response: a) The NMAs conducted by the EAG used a frequentist approach. These approaches do not use priors, therefore there was no need for the EAG to conduct such an assessment. b) There were no evidence loops containing both direct and indirect evidence. Therefore, such an analysis is not possible. This is very clear from observing the network diagram provided in the EAG report. 5) Use of random or fixed effects EAG response: The EAG examined both random and fixed effect models and found no difference between them.

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		of the analyses does not align with NICE methods guide or NICE NMMA reporting standards which states that *"The methods and results of the individual trials included in the network meta-analysis and a table of baseline characteristics for each trial must be documented."* and "*The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported. If inconsistency within a network meta-analysis is found, then attempts should be made to explain and resolve these inconsistencies."*[10,11] - **Wide confidence intervals**: The analyses were associated with wide confidence intervals which limit the ability to draw inferences from the analyses. As such, the analyses have limited use for decision making. **<u>Uncertainty in clinical validity of NMA results</u>** The results from the EAG exploratory NMA lack clinical validity as the comparative effectiveness of zanubrutinib versus venetoclax-based regimens flips between favouring zanubrutinib (previously untreated population) and favouring	6) Wide confidence intervals EAG response: Wide confidence intervals reflect uncertainty. Quantification of uncertainty is relevant to decision-making. 7) Uncertainty in clinical validity of NMA results EAG response: Whether this is the case or not is a matter of opinion. It is an uncertainty that needs further exploration.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		venetoclax-based regimens (R/R population). It would be more clinically reasonable for the direction of effect to be consistent across populations given that clinical trial data indicates that zanubrutinib is clinically effective across both previously untreated and R/R patients with CLL.	

Issue 2 Applicability of the SEQUOIA trial population to the previously untreated CLL comparison (EAG issue 3)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, Page 19, Table 1.4, Row 2: "the EAG has concerns about the categorisation of participants in Cohort 1 in SEQUOIA as "unfit" rather than "fit" due to these participants being eligible for BR." **Section 2, Page 40, Table 2.1, Row 6:** "The EAG considers that the categorisation of	The Company requests that the EAG rephrases these statements given that Cohort 1 of SEQUOIA is representative of "unfit" patients as demonstrated by the trial eligibility criteria and clinical expert opinion. Whilst the Company acknowledges that the definitions used in the	**<u>SEQUOIA eligibility criteria and comparison with other CLL trials</u>** The eligibility criteria for the SEQUOIA trial are akin to the eligibility criteria for the ELEVATE-TN trial and the eligibility criteria for the CLL-14 trial which are seen as representative of previously untreated "unfit" patients with CLL by NICE.[12,13] - **Key eligibility criteria for SEQUOIA**: Eligible patients were aged ≥65 years or, if 18-64 years, had a creatinine clearance below 70 mL/min, history of previous serious infection or multiple infections in the past 2 years and/or a	Thank you for highlighting. The EAG acknowledge the difficulty in defining "fitness" and have based its definition on the company's proposed placement of zanubrutinib within the clinical pathway (CS, Figure 1) and the BSH guidelines, which consider BR an acceptable alternative for "fit" patients for whom FCR is contraindicated.[4,5] As a result, this creates some ambiguity over participants in the SEQOUIA trial being considered "unfit".

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participants in Cohort 1 of the SEQUOIA study may be considered "fit" rather than "unfit," as they were eligible for BR" **Section 2.5, Page 44:** "The EAG has concerns surrounding the categorisation of participants in the SEQUOIA trial as "unfit." The company's definition of "unfit" is that participants would be unsuitable for treatment with FCR and BR, based on their placed of zanubrutinib in the clinical pathway (CS, Figure 1).[5] However, participants in SEQUOIA Cohort 1 were randomised to either zanubrutinib or BR but were ineligible for FCR (CS, Table 9).[5] By the company's definition, this means the population in SEQUOIA Cohort 1 are deemed to be "fit.""	CS were related on a patients ability to receive CIT, this definition was selected to align with the final NICE scope and definitions previously used by NICE to appraisal treatments in CLL and does not reflect clinical practice in its entirety especially when considering the recent update to the BSH guidelines in 2022 which no longer recommend bendamustine-based CIT as a first-line treatment option.	Cumulative Illness Rating Scale (CIRS) score > 6, meaning that patients were unsuitable for treatment with FCR-based therapy.[14] - **Key eligibility criteria for ELEVATE-TN**: Eligible patients were aged ≥65 years or, if younger than 65 years, had a CIRS-Geriatric score higher than 6 or renal dysfunction (creatinine clearance 30–70 mL/min), meaning that they would otherwise be unsuitable for FCR-based therapy.[12] - **Key eligibility criteria for CLL-14**: Eligible patients were aged 18 years or older, had previously untreated CLL, and coexisting conditions with a CIRS greater than 6, a creatinine clearance of 30–69 mL/min, or both.[15] In comparison, the key eligibility criteria for CLL10 which is seen as representative of previously untreated "fit" patients with CLL were contrasting. - **Key eligibility criteria for CLL10**: Eligible patients were required to have a low comorbidity burden as defined by a CIRS score ≤6, a normal creatinine clearance of ≥70 mL/min, and an	As the placement of zanubrutinib being incorporated in the clinical pathway (CS, Figure 1)[4] is what is being considered by the NICE committee the EAG are highlighting the discrepancy in the CS over the definition of "fitness" and hence the potential uncertainty in the applicability of the SEQOUIA data. However, the EAG appreciate that there is ambiguity over the definition of fitness and have reflected this in Section 2.5 (p.44) of the EAG report, "The EAG appreciate that the definition of "fitness" is non-binary and that, while BR is considered CIT, according to the BSH guidelines it is considered an acceptable alternative for "fit" patients for whom FCR is contraindicated."[5] In addition, to fully reflect the eligibility criteria of the SEQUOIA trial and the clinical factors that also need to be considered when looking at "fitness," the EAG have updated the text in Section 2.5 to include the additional eligibility

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Section 3.6, Page 113: "The EAG appreciates that evidence in the "fit" population is sparse but has concerns about the data from SEQUOIA Cohort 1 being used as a proxy for the "unfit" population." **Section 4.3.3, Page 126:** "The EAG has concerns about the categorisation of the SEQUOIA population, as the company define all participants in Cohort 1 as "unfit" but, due to their ability to be eligible for BR in the trial, the EAG considers the participants to be "fit." The participants' eligibility for BR also means they are considered "fit" by the standards of the BSH guidelines.[2] The EAG considers the paucity of evidence, particularly for the "unfit" untreated CLL patients without del17p		European Cooperative Oncology Group (ECOG) performance status of 0–2 for inclusion.[16] **<u>Regulatory support</u>** The European approval of zanubrutinib by the EMA confirms the applicability of the SEQUOIA patient population to the previously untreated "unfit" population: *"Despite inclusion exclusion criteria of study 304 [SEQUOIA] in the frontline setting clearly indicate that patients should have been unsuitable for treatment [with] chemoimmunotherapy (FCR), study 305 [ALPINE] showed noninferiority and superiority (based on INV assessment) against ibrutinib in the R/R setting. Having in mind that ibrutinib is also approved in 1L, and recommended in both fit and unfit patients, it seems justified to extrapolate the use of zanubrutinib to 1L fit patients. Thus, despite the limitations of study 304 and the comparison against BR in an elderly and unfit population, the totality of evidence supports the use of zanubrutinib in both fit and unfit patients."*[17]	criteria for patients under 65 years. Section 2.5 (p.44), has been updated with the following text: "However, the EAG acknowledges that patients randomised to the SEQUOIA trial were older (65 years and over), but, if they were 18 to 64 years, they had to have a creatinine clearance below 70 mL/min, history of previous serious infection or multiple infections in the past two years and/or a CIRS score > 6, and, while they were eligible for BR, they were not considered "fit" for intensive CIT." The EAG have included this additional information on the clinical eligibility criteria of the SEQUOIA trial so that NICE can assess Key Issue 3 using 1) the definition of fitness (CS, Figure 1)[4] and 2) the clinical profile of SEQUOIA participants. Ultimately it is up to the NICE committee to decide on whether the data from SEQOUIA is reflective of an "unfit" untreated CLL population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and/or TP53 mutation, to be a major source of uncertainty. This is partially addressed in the approach presented by the company, which utilises data on patients that would be considered as "fit" as a proxy for "unfit" untreated CLL patients" **Section 4.3.6.2.1, Page 133:** "However, large uncertainties remain about the relative efficacy of zanubrutinib versus acalabrutinib, particularly for the "unfit" sub-population, specifically in the area of disease progression. The uncertainty in the "unfit" sub-population is amplified by it being modelled after data from potentially "fit" patients from SEQUOIA (see Section 3.2.1.1) and the immaturity		**<u>Use of BR as a comparator</u>** BR was used as a comparator in the SEQUOIA trial because at the time of study design, the standard frontline treatment in patients without 17p deletion or TP53 mutation was CIT. BR was a commonly used standard treatment option for frontline "unfit" CLL patients without 17p deletion in the countries in which the trial was to be conducted.[18,19] in the UK, BR was recommended as an alternative treatment option for less "fit" patients with CLL by the BSH in their 2018 guidelines,[20] but has since been removed in the most recent 2022 guidelines. The choice of BR was agreed upon as a globally acceptable comparator with regulatory authorities, including the FDA and EMA. Results showing whether BTK inhibition could be superior to CIT (ALLIANCE and ECOG 1912) were not released until 2018 through early 2019.[21,22] Therefore, whether BTK inhibition was superior to CIT remained an open question at the time of study design. The ALLIANCE study was also the first randomised study showing concerning potential cardiac toxicities, including sudden cardiac death, associated with ibrutinib, which precluded that	

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of trial data (median follow-up is approximately 22.8 months in arm A and 27.7 months in arm C) means there were very few events observed."		ibrutinib should have been used as the comparator.[21]	

Issue 3 Uncertainty in the interpretation of MAIC results for survival outcomes in previously untreated CLL and R/R CLL, uncertainty in the previously untreated "high-risk" CLL subgroup and use of a cost-minimisation approach (EAG issues 4, 6 and 9)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1, Page 22 "EAG suggest that R/R CLL is not a suitable proxy for untreated "high-risk" CLL hence there is a lot of uncertainty in this assumption and the company cannot assume that the effectiveness of zanubrutinib compared with ibrutinib in patients with R/R CLL is also experienced by those with untreated "high-risk" CLL"	The Company requests that the EAG rephrases these statements given that data in R/R CLL has previously been accepted by NICE to inform comparisons in the previously untreated "high-risk" population and to highlight that additional supporting evidence was provided in the form of: - A MAIC versus acalabrutinib using ELEVATE-TN in previously untreated "high-risk" and non-"high-risk" CLL patients.	**<u>NICE has previously accepted evidence in R/R CLL as a proxy to support reimbursement decisions in "high-risk" previously untreated CLL</u>** In NICE TA689 and TA429 NICE agreed that data from the R/R setting is an appropriate proxy to inform the clinical effectiveness of two BTKis (acalabrutinib and ibrutinib) in the previously untreated "high-risk" population.[23,24] In appraisal TA429, NICE assessed ibrutinib for the treatment of previously untreated and previously	Thank you for highlighting. The EAG has updated the EAG report to reflect the additional evidence reported in the CS. Section 1, Table 1.7 (p.22) has been updated with the following text: "The company undertook a scenario analysis using data from their naïve comparison however the EAG consider these data to be subject to uncertainty due to the nature of this study being retrospective, and because potential confounding factors, such as age or IGHV mutation,

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Section 1, Page 23 **"**Furthermore, data comparing ibrutinib and zanubrutinib in untreated "high-risk" CLL patients is needed as using data from the R/R CLL clinical trials as proxy is subject to uncertainty (see Key Issue [9])." **Section 1, Page 28** "the EAG have concerns about the use of data from patients with R/R CLL being used as a proxy in untreated "high-risk" CLL." **Section 2, Page 39, Table 2.1, Row 5:** "The evidence for zanubrutinib versus ibrutinib in untreated CLL patients with del17p used R/R patient data as a proxy; based on clinical advice, this approach was not considered appropriate by the EAG,	- A naïve comparison vs. ibrutinib using Mato et al (2018): - Clinical expert opinion. Whilst Cohort 2 of SEQUOIA is among the largest bodies of prospective evidence collected specifically for patients with a 17p deletion, there is a paucity of evidence specifically reported in patients with 17p deletion and/or TP53 mutation for comparator treatments. As such, the Company has presented the best use of the data available within the CS.	treated patients with CLL. Despite the submitting company only presenting evidence of the efficacy of ibrutinib in previously treated CLL patients, the Committee accepted that data from previously treated patients could be considered and NICE recommended ibrutinib as an option for treated CLL in people who have had at least one prior therapy as well as in previously untreated patients who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable. In appraisal TA689, NICE assessed acalabrutinib for the treatment of previously untreated and previously treated patients with CLL. Similarly, data for previously treated CLL patients supplemented the approval of acalabrutinib as an option for previously untreated CLL patients that have a 17p deletion or TP53 mutation, given the lack of first-line specific "high-risk" data. **<u>Additional supporting data was provided in the CS which supports the efficacy of zanubrutinib in "high-risk" patients</u>**	were not controlled for in the comparison." Section 1, Table 1.7 (p.24) has been updated with the following text: "The company attempted to address this uncertainty by undertaking a scenario analysis using data from their naïve comparison however the EAG consider these data to be subject to uncertainty due to the nature of this study being retrospective, and because potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison." Section 1, Table 1.10 (p.27) has been updated with the following text: "The company also used data from their naïve comparison however, the EAG have concerns about the validity of this data due to the nature of this study being retrospective, and because potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison."

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as R/R is not a suitable proxy for "high-risk" (i.e. del17p or TP53 mutation)." **Section 4.3.2, Page 126-127:** "The EAG also notes that evidence of the relative efficacy of zanubrutinib versus ibrutinib in the untreated "high-risk" CLL population comes from a trial using data on R/R CLL patients only." **Section 5.1, Page 164:** "Also, the EAG have concerns with the effectiveness of zanubrutinib compared with ibrutinib in untreated CLL, given these data were based on the ALPINE trial which is in a R/R CLL population (see Section 4.3.4 and Section 4.3.6.2.3)."		Additional evidence to support relative efficacy of zanubrutinib versus ibrutinib in the previously untreated "high-risk" CLL population is provided in Section B.2.9.4.2 of the CS which the EAG have excluded from their report: **MAIC for zanubrutinib versus acalabrutinib using ELEVATE-TN in previous untreated CLL patients:** With the MAIC comparing zanubrutinib with acalabrutinib in previously untreated patients (using ELEVATE-TN) and the MAIC comparing zanubrutinib with acalabrutinib in patients with "high-risk" R/R CLL (using ELEVATE-RR) both demonstrating that PFS and OS between acalabrutinib and zanubrutinib is not statistically significantly different, it follows that zanubrutinib PFS and OS will not be statistically significantly different to ibrutinib within the previously untreated "high-risk" population.	Section 1, Table 1.10 (p.27) has been updated with the following text: "Based on the company's naïve comparison, which is subject to uncertainty, it is likely that zanubrutinib would still be considered cost-effective in this subpopulation." Section 2, Table 2.1 (p.39) has been updated with the following text: "Furthermore, in the company's naïve comparison using data from Mato *et al*., (2018) non-inferiority was not demonstrated for PFS (HR: [redacted]; 95% CI, [redacted], [redacted]) however there was a statistically significant difference in OS demonstrated between zanubrutinib compared with ibrutinib (HR: [redacted]; 95% CI, [redacted], [redacted])." Section 4.3.3 (p.128) has been updated with the following text: "The company also undertook a scenario analysis using data from their naïve comparison however the EAG consider these data to be subject to uncertainty due to the nature of this study being

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.2.1.2, Page 191: "….and the assumption by the company that data from R/R CLL is a suitable proxy for untreated "high-risk" CLL in the comparison of zanubrutinib with ibrutinib,…" **Section 4.3.6.2.2, Page 133:** "For the "high-risk" population, the company compared zanubrutinib with acalabrutinib across two different MAICs in patients with R/R CLL using data from ALPINE versus ELEVATE-RR or ASCEND (see Tables 4.10 and 4.11)."		- **Naïve comparison with ibrutinib using Mato et al (2018):** Mato et al. (2018) was a retrospective study identified within the clinical SLR which presented data on patients who did not meet the inclusion criteria for the RESONATE-2 study (specifically <65 and/or those with 17p deletion).The naïve comparison demonstrated that there was no statistically significant difference in PFS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted], [redacted]). However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted], [redacted]). - **Support from UK clinical advisors at an advisory board:** At an advisory board held by the Company (03 November 2022), UK clinicians deemed the conclusion that zanubrutinib will be at least non-inferior to	retrospective, and because potential confounding factors, such as age or IGHV mutation, were not controlled for in the comparison." Section 5.1 (p.166) has been updated with the following text: "Also, the EAG have concerns with the effectiveness of zanubrutinib compared with ibrutinib in untreated CLL, given these data were based on the ALPINE trial which is in a R/R CLL population and a naïve comparison" Section 6.2.1.2 (p.193) has been updated with the following text: "… and the uncertainty in the data used to inform the untreated "high-risk" CLL subpopulation analyses…" Section 4.3.6.2.2 (p.135) has been updated with the following text: "Results from the ELEVATE-TN MAIC could not be used to inform this subpopulation as trial results for the "high-risk" population of ELEVATE-TN were not reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		ibrutinib in previously untreated “high-risk” patients as clinically plausible.	independently. The company also highlights TA429 and TA689 as previous appraisals with a NICE recommendation (for acalabrutinib and ibrutinib respectively), where data for patients with R/R CLL were used to model a population of patients with del17p or TP53 mutation unsuitable to receive CIT.” The EAG have updated the EAG report to acknowledge the naïve comparison undertaken by the company using data from Mato *et al*., (2018)[6] However, the EAG still consider there to be uncertainty in the assumptions and data used to inform this subpopulation as outlined in Key Issue 9. In addition, the EAG do not consider the company’s justification that this assumption has previously been accepted by NICE in previous TAs to be sufficient. This assumption should be based on the clinical plausibility of R/R CLL being a proxy for “high-risk” untreated CLL. The clinical advisory board to the company

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			stated that it is likely that it is clinically plausible for zanubrutinib to be non-inferior to ibrutinib in "high-risk" untreated CLL however, there does not appear to the EAG to be any clinical justification on R/R CLL being a suitable proxy for "high-risk" untreated CLL. Ultimately it is up to the NICE committee to decide whether they consider R/R CLL to be a suitable proxy for "high-risk" untreated CLL in each individual appraisal.
Section 3.3.1, Pages 87 – 95 This section contains the indirect comparison for previously untreated CLL, however the naïve comparison conducted using data from patients with 17p deletion treated with ibrutinib from Mato et al. (2018) is missing from this section.	The Company requests adding the naïve comparison conducted using data from Mato et al. (2018). This is reported on page 144 of the CS, text as follows: "To supplement the comparison with ibrutinib, a naïve comparison was conducted to assess the efficacy of zanubrutinib with ibrutinib in patients with untreated CLL. Clinical efficacy for patients with 17p deletion treated with ibrutinib was extracted from Mato et al. (2018) and compared with Cohort 2 (arm C) of SEQUOIA.[25]	Missing information. The Company requests that the naïve comparison conducted using data from Mato et al. (2018) be included within this section to complement the MAICs conducted and provide supportive data for the previously untreated "high-risk" population.	Thank you for highlighting. The EAG has updated Section 3.3.1 of the EAG report to acknowledge the indirect comparison using data from Mato *et al*., (2018)[6] Section 3.3.1.1 (p.87) the following text was included: "The company also reported an additional study that included a comparison with ibrutinib to supplement the results of the MAICs (see Section 3.3.1.5)".

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	Mato et al. (2018) was a retrospective study identified within the clinical SLR which presented data on patients who did not meet the inclusion criteria for the RESONATE-2 study (specifically <65 and/or those with 17p deletion). As with the other MAICs, WebPlotDigitizer was used for digitisation, and the IPD from KM method was used for IPD generation and HR estimation. A formal MAIC was not conducted given that baseline characteristics for patients with a 17p deletion only, to align with the SEQUOIA eligibility criteria of Cohort 2 (arm C), were not published in Mato et al. (2018). Instead, an unstratified Cox regression models was used to estimate HRs for PFS, and OS. Based on this naïve comparison, there was no statistically significant difference in PFS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted]). However, there was a statistically significant difference in OS between zanubrutinib and		Section 3.3.1.5 (p.96) the following text was included: "The company also reported an additional study that included a comparison with ibrutinib as alluded to in Section 3.3.1.1. This was a naïve comparison assessing the efficacy of zanubrutinib with ibrutinib in patients with untreated CLL. Data on clinical efficacy for patients with 17p deletion treated with ibrutinib were extracted from Mato *et al*., (2018) and compared with Cohort 2 (arm C) of SEQUOIA. Mato *et al*., (2018) was a retrospective study identified within the clinical SLR which presented data on patients who did not meet the inclusion criteria for the RESONATE-2 study (specifically <65 years and/or those with 17p deletion). A formal MAIC was not conducted given that baseline characteristics for patients with a 17p deletion only, required to align with the SEQUOIA eligibility criteria of Cohort 2 (arm C), were not published in Mato *et al*., (2018).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	ibrutinib (HR: [redacted]; 95% CI, [redacted]).”		Instead, an unstratified Cox regression model was used to estimate HRs for PFS and OS. Based on this naïve comparison, there was no statistically significant difference in PFS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted], [redacted]). However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib (HR: [redacted]; 95% CI, [redacted], [redacted])”. Section 3.1.1.5 (p.96) the following text was included: “The EAG acknowledge that the company conducted a naïve comparison using data from Mato *et al*., (2018) to complement the MAICs and to provide supportive data for the previously untreated “high-risk” population, but note that the study was retrospective, and at risk of potential confounding bias as factors such as age and IGHV mutation were not controlled for in the comparison”.[7]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, Page 20, Table 5, Row 2: "The EAG consider the company's conclusions in the MAIC analyses confuse a lack of statistical significance with non-inferiority or equivalence". **Section 1.5, Page 22, Table 1.7, Row 1**: "[Untreated CLL] The EAG does not consider that the MAIC results provide sufficient evidence of non-inferiority (see Key Issue [4]), hence a CUA approach is considered more appropriate to represent the decision problem." "R/R CLL: As with untreated CLL, evidence of from the MAIC results was insufficient to convincingly justify a CMA approach between	The Company requests that the EAG rephrases these statements to acknowledge that the approach the Company took assuming equal efficacy vs alternative BTKis despite showing improved outcomes was conservative. Given the wide confidence intervals on the MAIC analyses, the Company was wary of basing the clinical and cost-effectiveness arguments on the MAIC outputs. Whilst the MAICs highlighted an improvement in PFS in all models, the Company took the conservative assumption of equalising the efficacy of zanubrutinib and alternative BTKis to avoid introducing additional uncertainty into the submission. In using a CMA approach, the Company equalised efficacy and safety despite showing improved outcomes for patients treated with zanubrutinib, which is conservative. As such, the wording within the report should be updated to reflect that this assumption is conservative.	**NICE has previously accepted the use of a CMA approach to support reimbursement decisions in CLL** In appraisal TA689, the submitting company undertook an unanchored MAIC to compare acalabrutinib with ibrutinib in patients with previously treated R/R CLL. A statistically significant difference was not demonstrated for PFS or OS between the two treatments, resulting in the submitting company concluding that the results of the MAIC demonstrate that the efficacy of acalabrutinib in PFS and OS in patients with R/R CLL is at least equivalent to that of ibrutinib. The EAG concluded that it was reasonable to assume clinical equivalence of acalabrutinib and ibrutinib in the population with previously treated R/R CLL. Results from the MAIC were used to justify the use of a CMA approach for decision-making and this approach was accepted by the Committee. Furthermore, the NICE methods guide reports that a CMA approach "*can be used when the health effects of an intervention are the same as*	Thank you for highlighting. The EAG acknowledge throughout the EAG report that the company assuming equal efficacy versus alternative BTKis was conservative in the comparison of zanubrutinib with ibrutinib in R/R CLL. However, for all of the other comparisons, while the point estimates may favour zanubrutinib, the wide confidence intervals included a clinically meaningful difference. This uncertainty associated with the effectiveness of zanubrutinib should have been incorporated into the economic analysis. NICE might have previously accepted the use of a CMA and the guidance around its use as quoted by the company is that it "*can be used when the health effects of an intervention are the same as those of the status quo"* In this situation the equivalence (and non-inferiority can be

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
zanubrutinib and acalabrutinib" **Section 4.3.2, Page 126:** "the EAG considers that uncertainty in the relative efficacy of zanubrutinib does not provide concrete evidence of non-inferiority, therefore undermining the core assumptions of the CMA." **Section 4.3.10, Page 145, Section 4.4.10. Page162, Section 5.1. Page 164, Section 5.2, Page 177, Section 6.3.5, Page 234:** "The EAG considers a CUA approach to be more appropriate than the CMA approach used by the company as the best representation of the decision problem" **Section 4.4.6, Page 155:**	Furthermore, the plausible equivalence or improved treatment effect of zanubrutinib compared to alternative BTKis is supported by direct clinical evidence, UK expert opinion and NICE precedent reimbursement decisions and not solely based on the MAIC results which should be reflected in these statements. In addition, the Company requests that the report is updated to acknowledge that the Company performed multiple CUA scenario analyses, as presented in Table 96, Section B3a.11.3 and Table 125, Section B3b.11.3 of the CS, to alleviate any uncertainty. In total, the Company presented: - seven CUA scenario analyses comparing zanubrutinib to acalabrutinib in the previous untreated population, - two CUA scenario analyses comparing zanubrutinib to ibrutinib in	*those of the status quo"* and as such, formally proving non-inferiority is not a requirement for the use of this approach.[10] **<u>The results of the ALPINE trial and clinical expert opinion support the plausible equivalence of zanubrutinib compared to alternative BTKis</u>** In ALPINE, zanubrutinib demonstrated a statistically significant improvement in the primary endpoint of INV assessment overall response rate (ORR) and key secondary endpoints, including PFS and duration of response (DOR), when compared to ibrutinib in patients with R/R CLL. This makes zanubrutinib the first BTKi to demonstrate superiority against a comparator BTKi on a clinically meaningful endpoint. OS data from ALPINE is immature; however, OS appears to favour zanubrutinib over ibrutinib.[26] In the ELEVATE-RR trial, acalabrutinib demonstrated non-	considered to provision of evidence that the interventions are not materially different) was not demonstrated for all comparisons and all relevant health effects (except when zanubrutinib was compared in ibrutinib in R/R CLL). Hence the assumptions required for a valid CMA are not fulfilled and the analysis was not compliant with NICE guidelines on the use of CMA. The EAG acknowledge that the adoption of a CUA over the CMA approach used may not change the conclusions. However, the EAG cannot be certain of this due to limitations with the model. The EAG have updated the EAG report to reflect this. Section 1.5, Table 1.7 (p.22) has been updated with the following text: "The EAG acknowledge that the adoption of a CMA over a CUA may not materially change conclusions, as demonstrated from the EAG's base-case analyses. However, the EAG cannot be certain of this as the

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"the EAG considers that a CUA would have been more appropriate in this comparison than the CMA approach the company adopted" **Section 6.2.1, Page 191L** "the EAG consider the assumption on non-inferiority to be unjustified and hence consider the CMA approach adopted by the company to be a violation of accepted best practice."	the previous untreated population, - two CUA scenario analyses comparing zanubrutinib to acalabrutinib in the R/R population, - two CUA scenario analyses comparing zanubrutinib to ibrutinib in the R/R population.	inferiority to ibrutinib in previously treated patients with CLL.[27] Given that the ALPINE trial showed clinical superiority of zanubrutinib over ibrutinib, and the ELEVATE-RR trial showed acalabrutinib to be non-inferior to ibrutinib, it follows that it is plausible to assume that zanubrutinib is at least clinically equivalent to acalabrutinib, which is what is required to justify the CMA approach. This is reflected in the definition published by the University of York which states, "*Cost minimisation analysis is a method of comparing the costs of alternative interventions (including the costs of managing any consequences of the intervention), which are known, or assumed, to have an equivalent medical effect.*"[28] UK clinical experts in attendance at an advisory board (03 November 2022) deemed the conclusion that the treatment effect of zanubrutinib is at least equivalent compared to alternative BTKis as clinically plausible.[3]	company's economic model was structured to undertake a CMA and hence there are limitations associated with the CUAs undertaken by both the company and EAG." Section 1.7 (p.29) has been updated with the following text: "The adoption of a CUA as the company's base-case may not have changed the conclusions but as a result of this assumption, there is uncertainty in some of the parameters included in the economic model, which the EAG tried to explore in scenario analysis." Section 4.2.1, Table 4.5 (p.123) has been updated with the following text: "The adoption of a CUA as the company's base-case may not have changed the conclusions but the EAG cannot be certain of this due to limitations with the modelling associated with the CMA assumption." Section 4.3.10 (p.147): Has been updated with the following text:

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		<u>The use of CMA is conservative as demonstrated by the EAGs preferred base case</u> The EAG opted to use HRs derived from the Company's MAICs to inform their preferred base case. In the previously untreated CLL population, zanubrutinib is associated with a quality-adjusted life-year (QALY) gain in the EAG base case when compared with acalabrutinib and ibrutinib. Similarly, in the R/R CLL population, zanubrutinib is associated with a QALY gain in the EAG base case when compared with ibrutinib. As a conservative approach, the Company assumed no QALY gain was associated with zanubrutinib and assumed all treatments had equal efficacy. The conservativeness of this approach is reflected in the cost-utility scenario analyses conducted by the Company, as presented in Table 96, Section B3a.11.3 and Table 125, Section B3b.11.3 of the CS. In the previously untreated population, zanubrutinib dominated acalabrutinib	"The EAG acknowledges the adoption of a CUA as the company's base-case may not have changed the conclusions, as illustrated by the CUAs undertaken by both the company, in scenario analyses (see Section 5.1.1.2) and the EAG in their base-case analysis (see Section 6.2.1). However, the EAG cannot be certain of these conclusions due to limitations with the modelling associated with applying a CUA to this economic model (see Section 4.3.2.1). The EAG attempted to address this uncertainty by considering alternative assumptions which maximised all the data available and arguably produced more robust estimates of cost-effectiveness (see Section 6.2.1.2)." Section 4.4.6.2.1 (p.157) has been updated with the following text: "The EAG acknowledges the adoption of a CUA as the company's base-case may not have changed the conclusions, as

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		in all seven CUA scenario analyses conducted by the Company. Furthermore, zanubrutinib dominated ibrutinib in both CUA scenario analyses conducted. In the R/R population, zanubrutinib dominated acalabrutinib in the two CUA scenario analyses using the ELEVATE-RR MAICs and was cost-effective in the two CUA scenario analyses using the ASCEND MAICs. When taking an average of all four CUA scenarios across the ELEVATE-RR and ASCEND MAICs, zanubrutinib dominated acalabrutinib. In addition, zanubrutinib dominated ibrutinib in the CUA scenario using directly extrapolated data from ALPINE. These results were consistent when tested both deterministically and probabilistically. By varying the MAIC HRs in accordance with the uncertainty of the respective distributions, the probabilistic analysis accounts for the uncertainty in the HRs between zanubrutinib and acalabrutinib and between zanubrutinib and ibrutinib. As	illustrated by the CUAs undertaken by both the company, in scenario analyses (see Section 5.2.1.2) and the EAG in their base-case analysis (see Section 6.3.1). However, the EAG cannot be certain of these conclusions due to limitations with the modelling associated with applying a CUA to this economic model (see Section 4.4.2.1)." Section 4.4.10 (p.164) has been updated with the following text: "Henceforth, the EAG does not consider a CMA to be the best approach to represent the decision problem the decision problem in the comparison of zanubrutinib with acalabrutinib The EAG acknowledges the adoption of a CUA as the company's base-case may not have changed the conclusions, as illustrated by the CUAs undertaken by both the company, in scenario analyses (see Section 5.2.1.2) and the EAG in their base-case analysis (see Section 6.3.1). However, the EAG cannot be certain of these

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		outcomes still favoured zanubrutinib when run probabilistically, it is plausible to assume that zanubrutinib is at least clinically equivalent to acalabrutinib and ibrutinib.	conclusions due to limitations with the modelling associated with applying a CUA to this economic model (see Section 4.4.2.1)." The EAG have updated the EAG report to acknowledge the CUA approach adopted by the Company as scenario analyses. Section 4.3.2 (p. 127) has been updated with the following text: "The EAG is aware that a CUA approach was proposed by the company as a scenario analysis by using the PFS HRs from the MAIC as a replacement for time to disease progression (TTP) HRs for acalabrutinib." Section 5.1 (p.166) has been updated with the following text: "The EAG considers a CUA approach, which the company adopted in scenario analyses (see Section 4.3.2.1 and Table 5.2), to be more appropriate than the CMA approach used by the company in their basecase analysis as the

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			best representation of the decision problem (see Section 4.3.6.2)." Section 5.2 (p.179) has been updated with the following text: "Therefore, the EAG considers a CUA approach, which was adopted by the company in scenario analyses, to be more appropriate than the CMA approach used by the company in their base-case analysis as the best representation of the decision problem (see Section 4.4.6.2)." Section 6.2.1.2 (p.193) has been updated with the following text: "A CUA approach was adopted by the company in scenario analyses (see Section 5.1.1.2). The EAG critiqued the approach presented by the company (see Section 4.3.2.1) and considers alternative assumptions which maximise all the data available and would produce more robust estimates of cost-effectiveness (see Section 6.2.1.2)." Section 6.3.5 (p.236) has been updated with the following text:

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			“The company did adopt a CUA approach as a scenario analysis for both pairwise comparisons across six scenario analyses.”

Issue 4 Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies clinical and HRQoL studies of interest in previously untreated CLL and R/R CLL and uncertainty in the utility estimates used in the economic models (EAG issues 2, 5 and 7)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1.1, Page 47: "On closer inspection, the EAG identified that the original SIGN RCT study type filter had been modified to exclude conference abstracts and conference proceedings from the filter. The company did not provide a rationale for this alteration, nor did they report this alteration in the search methods. The EAG understands that these two lines had been removed from the filter to not exclude conference abstracts from the search (as the original filter excludes this type of studies)." "The company did not provide separate full search strategies for each of the databases searched to locate conference papers and/or conference meeting webpages and, as such, the EAG is unable to comment on the ability of the reported searches to retrieve	The Company requests for these statements to be updated as conference proceedings and abstracts were included in the SLR. The first paragraph listed offers a contradiction in that it is claimed that the Company *"exclude conference abstracts and conference proceedings"* whereas the following sentences outline that the amendments to the filters were made to *"not exclude conference abstracts from the search (as the original filter excludes this type of studies)"* As conference abstracts and conference proceedings were included within the scope of the SLR and were not omitted as part of the search filter, there is no need to conduct a separate search for conference abstracts and conference proceedings. As such, the following two sections	The Company did not exclude conference abstracts or proceedings. It can be seen from the results that conference abstracts were indeed picked up by the SLR.	Thank you for highlighting. Section 3.1.1 (p.47) has been updated with the following text (with the key change in the last sentence in bold): "On closer inspection, the EAG identified that the original SIGN RCT study type filter would have excluded conference abstracts and conference proceedings as these types of studies are excluded in the original RCT filter designed by SIGN. In order to avoid the exclusion of these publication types, the company cut out the two lines from the RCT filter which referred to conference abstracts and proceedings. This manipulation would have resulted in conference abstracts and proceedings being present in the final set of results once the filter was combined with the PICOs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
relevant, up-to-date conference abstracts” “Since the reported search strategy in Embase.com used an RCT filter, it is unclear whether the reported search strategy would have identified all relevant conference papers from the conferences the company considered and listed as useful.”	of the report should be amended or removed as appropriate. Furthermore, all other related sections within the report should also be revised.		elements of the search. The EAG would like to note that the company did not provide a rationale for this filter alteration, nor did they report this alteration in the search methods. The EAG understands that these two lines had been removed from the filter to **not exclude** conference abstracts from the search (as the original filter excludes this type of studies).” Section 3.1.1 (p.48) has been updated with the following text: “This means that if a conference paper was indexed in Embase based on its topic-specific index terms (e.g., CLL) but did not include any RCT-specific index term, this paper would have been automatically excluded from the final set of results as per the company’s search approach. Since the reported search strategy in Embase.com used an RCT filter. Therefore, the EAG remains it is unclear as whether

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			the reported search strategy would have identified all relevant conference papers from the conferences the company considered and listed as useful." The EAG have updated the EAG report to acknowledge that the company removed the search lines from the SIGN RCT study filter which were aimed at excluding conference abstracts and proceedings. Regarding the sensitivity of the searches to retrieve all relevant conference abstracts the EAG does not claim that the company did not include conference abstracts from the final set of Embase.com results (refer to paragraph above). In the clarification letter the EAG requested the company to provide whether alternative methods (e.g., hand searching conference websites) were used to locate up-to-date conference abstracts. As the company did not elucidate, the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			EAG included the following critique in the report in Section 3.1.1 (p.48) "the EAG has concerns that the reported method for identifying relevant conference abstracts has not been robust enough and considers that, alongside the use of specific search approaches for Embase, manual hand searching of relevant conference sites should have been performed and reported as per the PRISMA standards recommend." The EAG critique of the company's method for locating relevant conference paper is in line with current recommended standard methods for undertaking good quality systematic literature searches.
Section 1.4, Page 18, Table 1.3, Row 1 "All searches for the identification of clinical studies lacked sensitivity,	The Company requests that these statements are removed.	Based on the guidance on the NICE website:[29] "If a decision has been taken to limit a review to studies reported in English, the	Thank you for highlighting. The Company has cited PMG15 "Interim methods guide for developing good practice guidance" (2014) [8] a process

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
were limited to English language only or publications from the UK" **Section 3.1.1, Page 49, Table 3.2, Row 12:** "The EAG assumed the exclusion of studies not reported in English was due to generalisability to a UK setting being sought. However, this may be a cause of selection bias in identifying relevant treatments in the network." **Section 3.1.2, Page 50:** "The company restricted the SLR to studies reported in English, which may present a bias.[7] The EAG is unable to assess the possible effect of excluding non-English studies on the SLR results."		appropriate database limit function can be used to improve precision". The Company used the appropriate function in the Embase database to restrict to publications reported in English. The restriction was put in place to allow all publications to be reviewed without the requirement for translators. Furthermore, restricting publications to those reported in English does not restrict publications to those published with a UK setting.	guidance developed by NICE and aimed at NICE teams developing NICE guidance to support their rationale to restricting publications to the English language. However, in the CS there was no rationale provided for the decision to exclude non-English language evidence. There is potential bias associated with this decision hence no changes were made to the EAG report on this regard. However, the EAG acknowledge that the company restricted studies to the English language and not the UK and have updated the EAG report to reflect this. Section 1.4, Table 1.3 (p.18) has been updated with the following text: "All searches for the identification of clinical studies lacked sensitivity and were limited to English language only". Section 3.1.2, Table 3.2 (p.50) has been updated with the

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			following text: “The EAG assumed the exclusion of studies not reported in English was due to pragmatic reasons. However, this may be a cause of selection bias in identifying relevant treatments in the network.”
Section 1.4, Page 18, Table 1.3, Row 1 “There are concerns with the currency of the evidence presented as searches were conducted at least nine months ago” **Section 3.1.1, Page 47:** “The reported date of searching being at least nine months ago raises concerns surrounding the currency of the evidence included in the submission.” **Section 4.1.1, Page 117:** “As also discussed in Section 3.1.1, the reported date of search being at least nine months ago raises issues with the currency of the evidence included in this submission.	The Company requests that these statements be removed or reworded to highlight that the Company’s SLR was in line with NICE methods as the current wording is misleading.	The Company’s SLR was conducted within 6 months of submission in line with the NICE methods guide.[10] Whilst the Company appreciates that the SLR is now 9 months old given the timelines associated with the NICE process, the SLR was conducted in line with NICE requirements and all references to the SLR being 9 months old should be removed as so not to give the impression that the SLR was not aligned with NICE methods.	Thank you for highlighting. The comment from the EAG was a factual annotation based on the reported search date which does not imply that the company did not follow the NICE methods guide (PMG36) [8]. Section 1.4, Table 1.3 (p.18) has been updated with the following text: “Despite alignment with the NICE methods guidance (PMG36) there are concerns with the currency of the evidence presented as searches were conducted at least nine months ago.” Although the EAG cannot identify where the NICE PMG36 recommends a period

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
According to established guidelines for conducting technology assessments, “it is recommended that if the assessment is to serve as a basis for healthcare decision-making, this period should be as short as possible. Ideally less than 6 months before publication”.[9]”			of 6 months from the date of searching to the date of submission to NICE for appraisal, the EAG understands that literature searches are usually undertaken at the start of a TA and may become soon out of date by the end of the TA process. However, there are mechanisms for keeping on top of emerging evidence such as alerts or running an update to the search towards the end of the SLR process which may mitigate some of the risks that lack of currency may pose to the evidence synthesis. The following European methodological guideline for information retrieval processes for systematic reviews and HTA on clinical effectiveness recommends that “if the assessment is to serve as a basis for healthcare decision-making, this period should be as short as possible. Ideally

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			[…] less than 6 months before publication." [9]) Section 3.1.1 (p.47) has been updated with the following text: "The EAG acknowledge that this may be a common concern of the HTA process and its variable timelines." Section 4.1.1 (p.118) has been updated with the following text: "The EAG acknowledge that this may be a common concern of the HTA process and its variable timelines."
Section 1.3, Page 17: "Firstly, if the company's SLR was updated to ensure all relevant data, including clinical trial data, on the effectiveness of VenR is captured." **Section 3.1.1, Page 50:** "The EAG disagree with the exclusion of VenR in the SLR for reasons outlined in Section 2.3."	The Company requests that all statements referring to VenR and VenO being excluded from the SLR are removed or updated to reflect that these treatments were captured within the SLR, but data were not extracted as the Company did not deem VenR and VenO to be relevant to the decision problem. For example, the text on page 95 should be updated to:	The Company would like to clarify that VenR and VenO were not excluded as comparators in the SLR as all relevant data for these treatments were collected in the SLR. However, as the treatments were not considered comparators as part of the CS, data from the studies identified in the SLR were not extracted as they were not deemed relevant.	Thank you for highlighting. Section 1.3, Table 1.2 (p.17) has been updated with the following text: "Firstly, if the company's submission was updated to ensure all relevant data, including clinical trial data, on the effectiveness of VenR was extracted from the SLR". Section 3.3.2.1 (p.97) has been updated with the following text: "As a consequence of the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"the EAG have concerns surrounding the exclusion of VenR and VenO in the SLR" **Section 3.3.2.1, Page 95:** "As a consequence of the company excluding VenR and VenO as comparators in the SLR, as previously discussed these treatments were not included as a comparator in any of the MAIC analyses."	"As a consequence of the company excluding VenR and VenO **as relevant comparators in the submission**, as previously discussed these treatments were not included as a comparator in any of the MAIC analyses."	It should also be noted that the EAG note this in the report in Section 3.1.2, page 50: *"The SLR conducted was broader than the scope of the CS and, as such, the company only extracted studies if they included zanubrutinib, acalabrutinib or ibrutinib as the treatments of interest.[5] The comparators included in the SLR were relevant to the NICE scope,[10] with the focus being on comparisons involving zanubrutinib, acalabrutinib and ibrutinib"*	company excluding VenR and VenO as relevant comparators in the submission […]" Section 3.1.2 (p.50) the text referring to VenR and VenO has been removed. Section 3.1.3 (p.50) has been updated with the following text: "The EAG disagree with the exclusion of extracted data on VenR from the SLR results within the submission, for reasons outlined in Section 2.3. As also documented in Section 2.3, VenO is a recommended option for initial therapy in patients unsuitable for CIT and, thus, it is not possible from the company analyses to assess the effectiveness of zanubrutinib compared with these interventions as data were not extracted. The EAG explored this uncertainty in Section 3.5".

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, Page 18, Table 1.3, Row 1 "[All searches] did not consider a comprehensive range of grey literature sources" **Section 3.1.1, Page 45:** With regards to grey literature searching: "This search was limited to "2 years" but the years that the search was limited to were not specified" **Section 3.1.1, Page 45, Table 3.1, footnote:** "No precise dates given for the start of the search date range, the search string shows limitation applied for 2 years (CS, Appendix D, Table 6)"	The Company requests that the text on page 45 is updated as follows: "This search was limited to within "2 years" **from the date of the searches"**	The grey literature search was limited to within 2 years of the search date.	Thank you for highlighting. The EAG would like to note that the company is providing additional information on the time limits imposed to their search for grey literature on the NICE and SMC websites that was not available to the EAG at the time of appraisal. The EAG have however accepted this change in support for clarity. Section 3.1 (p.45) has been updated with the following text: "This search was limited to "2 years" up to the search date."
Section 3.1.1, Page 46: With regards to the database used to conduct the SLR: "In their response, the company noted only one search needed to be performed within the Embase interface and all necessary information had been provided.[11]	The Company requests that the text on page 46 is updated as follows: "In their response, the company noted only one search needed to be performed within the Embase interface and all necessary information had been provided.[11]	The Embase interface searches the Embase, EMBASE Classic and MEDLINE databases simultaneously using one search strategy and as such, there is no need to use separate search strategies to	Thank you for highlighting. The EAG understands that according to the information provided by the Company in the CS Appendix D, a unique search on Embase.com was performed searching across three different databases

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Since the company did not conduct separate searches for Embase, MEDLINE, Embase Classic databases, the EAG was not able to quality check individual strategies against the databases reported." **Section 3.1.1, Page 46:** "The EAG notes that one of the databases used, 'Embase Classic' is a back file covering citations between 1947 and 1973; the company confirmed this within the clarification letter response,[11] which leads the EAG to question the relevancy of this source to the decision problem, as the company imposed publication date limits between 2007-2022 for which they provide a rationale in CS Appendix D" **Section 3.1.1, Table 3.1, Column 6, Row 2:** With regards to the Embase search strategy: "Partially"	The **Embase interface covers the Embase, EMBASE Classic and MEDLINE databases.** ~~Since the company did not conduct separate searches for Embase, MEDLINE, Embase Classic databases, the EAG was not able to quality check individual strategies against the databases reported~~." Furthermore, the Company also requests that the critique of searching Embase Classic is removed as Embase Classic is searched as part of the Embase interface search. The Company requests that this text in Section 3.1.1, Table 3.1, Column 6, Row 2 is updated to: "Yes" The Company requests that N hits per line is merged to present one 'Yes' for Embase, MEDLINE and Embase Classic.	search the individual databases.	(Embase, MEDLINE and Embase Classic). Nevertheless, in the clarification letter to the company the EAG wanted to clarify if separate search strategies had been performed via Embase.com. Since the company corroborated in their response to the clarification that one unique search was performed in Embase.com to search across the three databases, the EAG could only apply the PRESS checklist to this one strategy. The EAG is stating in Section 3.1.1 (p.46) that individual PRESS checklists could not be undertaken for each individual database (which would be considered best practice) as only one search strategy was applied to Embase.com. The EAG were unable to fully critique the search as it was undertaken through Embase.com, which is not standard practice, and have

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	These amendments should also be followed through into Table 4.1, page 116.		updated the EAG report accordingly. Section 3.1.1 (p.46) has been updated with the following text: "The EAG would like to acknowledge that the use of Embase.com to interrogate MEDLINE and Embase databases is not a standard and that there are other database platform providers such as OVID that allow access to such databases. The EAG does not have access to Embase.com because it is not freely available hence why the EAG requested individual search strategies for each database. Given that the EAG are unable to assess the quality of the search strategy used by the company the EAG are unable to verify that all relevant studies were identified across the different databases from this one search. The following comments from the EAG, which are based on best practice guidelines, are relating to the

			search process undertaken and the assumptions made as part of that search." With regards the request to remove the EAG critique on the company searching Embase Classic, the EAG is unsure whether the company could have done anything about not searching Embase Classic as the company seems to suggest that this database is searched simultaneously independently of its relevance to the search limits. The EAG has only appraised the evidence that the Company has submitted. In this they declare that Embase Classic was searched as part of their SLR, hence the EAG observation. No changes have been made to the EAG report. The EAG report has been amended in Table 3.1 and Table 4.1 to present one 'Yes' for Embase, MEDLINE and

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			Embase Classic as one SLR was provided.
Section 3.1.1, Page 48: "Concerns surrounding a single literature search encompassing different databases"	The Company requests that this statement is removed.	It is common practice to perform a single integrated SLR with integrated searches having been accepted in past appraisals (for example NICE TA673 [integrated clinical, cost-effectiveness, HRQoL an cost and resource use SLR] and TA689 [integrated cost-effectiveness, HRQoL an cost and resource use SLR][12,30])	The EAG have not commented on this except as a matter of judgement. The point which the company is aiming to clarify from the EAG critique, and the amendments and justification provided do not seem to correlate. The EAG wonders whether the Company is confusing SLR with systematic literature searches. No changes to the report have been made as the suggested amendment to the text is not addressing a factual inaccuracy.
Section 3.1.1, Page 46: With regards to search terms: "additional alternative drug names/codes could have been used that would have impacted on the number of records retrieved"	The Company requests that this statement is removed.	The Company used both branded and generic names for the intervention and comparators of interest in the search terms as indicated in Table 1, Index 2, Appendix D of the CS. Exploded search terms were also used for the generic drug names meaning	Thank you for highlighting. For a SLR to be comprehensive, the searches should aim to maximise sensitivity (the ability to retrieve as many as possible results). When searching for drug names and pharmaceuticals, it is common practice to include

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		any words or phrases associated with the generic drug names will have been captured. As such, it is unlikely that any key publications would have been missed.	all possible drug aliases and development names by which the drug would have been known before gaining its commercial name at the point of regulatory approval. The EAG's comment here refers to the fact that additional drug aliases could have been used to maximise the sensitivity of the searches which would have resulted in a higher yield of results. No changes to the report have been made.
Section 3.1.1, Page 46: "Furthermore, the EAG considers that using only one search term, "CLL," in non-bibliographic databases where no indexing or controlled vocabulary mapping of free-text terms occurs, such as the NICE and SMC websites, limits the ability of a search to retrieve all relevant records and that alternative spelling and search terms should have been considered."	The Company requests the following amendment: "Furthermore, the EAG considers that using only one search term, "CLL," in non-bibliographic databases where no indexing or controlled vocabulary mapping of free-text terms occurs, such as the NICE and SMC websites, limits the ability of a search to retrieve all relevant records and that alternative spelling and search terms should have been	The Company requests that the following section is updated to clarify that all relevant appraisals were captured using the CLL filter. As the NICE and SMC websites consistently list past appraisals, the Company did not see a need to test alternative search filters.	The EAG have not commented on this except as a matter of judgement. The EAG comment on this particular point is based on the evidence presented by the company in CS, Appendix D, of how these sources were searched. The EAG cannot verify if "all relevant NICE and SMC appraisals were considered within the appraisal" based on the reported search

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	considered. **However, it should be noted that all relevant NICE and SMC appraisals were considered within the appraisal.**"		method used to locate this evidence. In addition, the use of "CLL" rather than 'chronic lymphocytic leukaemia' as a search term means that potential studies could have been missed from this search hence the EAG cannot verify that "all relevant NICE and SMC appraisals were considered within the appraisal". No changes to the report have been made.
Section 4.3.8.2, Page 139: **"**The CS states that a PD utility value of 0.60 has been accepted in a number of previous NICE appraisals in CLL but do not provide references to support this statement.[4]"	The Company requests that this statement is removed.	In Section B.3a.4.6 of the CS, the second paragraph explains that a PD utility value of 0.60 was accepted in the NICE TA689 acalabrutinib submission.[12]	Thank you for highlighting. Section 4.3.8.2 (p.142) has been updated with the following text: "The CS states that a PD utility value of 0.60 has been accepted in a previous TA(TA689)."

Issue 5 Cost-effectiveness analyses conducted by the EAG and immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL (EAG issue 8)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Previously untreated CLL population			
Section 5.1.1.2, Page 166: "The list of parameters or assumptions changed in scenario analysis include the following: • Discount rate • TTP endpoint (INV-assessed) • TTP/PrePS curve for zanubrutinib • Use TTTD data for zanubrutinib • PPS cur7ve for BTKi • Exclude wastage • Exclude AE costs • Apply AE impact to QALYs	The Company requests the text to be amended to: "The list of parameters or assumptions changed in scenario analysis include the following: • Discount rate • TTP endpoint (INV-assessed) • TTP/PrePS curve for zanubrutinib • Use TTTD data for zanubrutinib • PPS curve for BTKi	The Company also presented two scenarios varying the 2L PFS curve for BTKi treatments, and nine CUA scenario analyses. These have been omitted from the EAG's description of the Company's scenario analyses.	Thank you for highlighting. The EAG have made the change suggested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Unfit/high risk data”	• **2L PFS curve for BTKi** • Exclude wastage • Exclude AE costs • Apply AE impact to QALYs • “Unfit/high-risk” data **within the CMA framework** • **CUA using pooled data from SEQUOIA Arm A and Arm C, applying HRs derived from ELEVATE-TN MAIC (Model 1 and Model 2) Mato et al.**		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	(2018) comparison and R/R data as a proxy. • **CUAs using Arm A and Arm C data separately applying HRs derived from ELEVATE-TN MAIC (Model 1 and Model 2), Mato et al. (2018) comparison and R/R data as a proxy."**		
Section 6.2.1, Page 191: **"How this violation was addressed by the EAG:** Unlike the approach employed by the company in Scenarios 15-21	The Company requests an update to the methods used, and subsequently the write up and results presented as part of the EAGs analyses to reflect that it is incorrect to apply an	PFS is defined as time to the first documented date of progression or death. TTP and PrePs endpoints are derived from the PFS data, with TTP representing the progression events (death events censored) and PrePS representing the pre-progression death events (progression events censored) within the dataset.	Thank you for highlighting. The EAG acknowledges that OS and PrePS are different endpoints and accepts this as a limitation to its approach. This assumption was made by the EAG to maximise all available data after considering the length of follow-up in SEQUOIA and the relatively low number of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
(Section 5.1.1), the EAG did not apply the HR estimates of PFS directly into the zanubrutinib parametric TTP curves to model the comparator TTP curves. Instead, the EAG applied the HR estimates of OS and PFS to modelled PrePS and TTP curves as follows: I. The HR estimate for OS from the MAIC between SEQUOIA[10] and ELEVATE-TN,[11] Model 1, was applied to zanubrutinib PrePS to derive the PrePS curve of acalabrutinib. The HR estimate for OS from the ALPINE trial[12] was used on the	OS HR to the PrePS endpoint, which is a function to PFS. Instead, a PFS HR should be used.	Therefore, to run the CUA it is appropriate to apply the PFS HR to both TTP and PrePS. The OS HR should not be applied to PrePS within the model given that PrePS is a function of PFS and not OS. The Company considers that the EAG have incorrectly applied the OS HR to the PrePS endpoint within the economic model.	OS death events across the arms treated with zanubrutinib in SEQUOIA [redacted] The EAG acknowledges that this is potentially a strong assumption and that it may present a more conservative scenario. Section 6.2.1.2 (p.194) has been updated with the following text: "The first caveat was the assumption that relative hazard estimates of OS can be applied to the current SEQUOIA PrePS data; the EAG adopts this assumption as the current follow up of the trial data is short and the number of OS death events was relatively low [redacted]. The EAG acknowledges that OS and PrePS are distinct endpoints, yet given the current absence of evidence this assumption makes the most of the available data while delivering a potentially conservative scenario. The EAG also presents a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
zanubrutinib PrePS curve to model ibrutinib PrePS. II. The TTP from zanubrutinib and the PrePS for acalabrutinib and ibrutinib were combined to generate PFS for each comparator respectively. III. The HR estimate for PFS from the MAIC between SEQUOIA[10] and ELEVATE-TN,[11] Model 1, was applied to the acalabrutinib PFS curve, to then derive TTP for acalabrutinib. Similarly, the HR estimate for PFS from the ALPINE trial was used on the PFS curve of			scenario where the impact of excluding OS HR estimates on the cost-effectiveness results is explored." An additional scenario analysis (Scenario 11) has also been added to assess the impact of removing OS HRs as inputs in the EAG base-case model. The EAG considers the approach undertaken for the EAG base-case model, while potentially conservative against zanubrutinib, makes the best use of all the available data which the EAG considered to be important given the paucity of evidence in this population. Section 6.2.3 (p.199) "The EAG base-case model makes the assumption that OS HRs obtained from the MAIC analyses were applicable to PrePS data from SEQUOIA.[4] As this has the potential to be a strong assumption over the long-term, the EAG explored an alternative CUA approach using only PFS HR estimates from the MAIC to predict survival in the comparator arms." Tables 6.4, 6.5 and 6.6 have been updated to incorporate this additional scenario analysis. In comparison with both acalabrutinib and ibrutinib, zanubrutinib remained the preferred treatment option as

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ibrutinib to derive TTP respectively.[12] The EAG acknowledges there were a number of caveats with this approach, starting with the assumption that relative effectiveness estimates of OS can be directly applicable to the current PrePS data, this assumption was not considered too strong due to the immaturity of the data in SEQUOIA,[10] and the fact that the competing risk of general mortality overtakes PrePS after the first 5 years in the model. Furthermore, this approach assumed that a partitioned-survival approach was appropriate to derive TTP from PFS. Although this was a strong			it was dominant (i.e., less costly and more effective in terms of QALYs gained).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
assumption, the EAG considers this approach to be the best use of all the data presented, considering the paucity of evidence for this population. Further limitations of this approach include the assumption of constant relative hazards over time, and that treatment effects have a lifetime duration, which add to the uncertainty around the results presented. An alternative scenario using Model 2 HR estimated from the MAIC between SEQUOIA[10] and ALPINE was also presented by the EAG as a less favourable comparison between zanubrutinib and acalabrutinib.“			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.2.1, Table 6.1, Page 193, row 4.	The Company requests that the EAG review and update row 4 in Table 6.1.	The presentation of this issue in its current form within Table 6.1 suggests that the Company did not perform scenarios for the extrapolation of TTP, and that the EAG have resolved this issue through its own scenarios. The Company presented two scenarios which explored alternative TTP distributions (see Table 95 of CS), and hence this issue has not been solely resolved by the EAG but was also addressed by the Company within the original submission.	Thank you for highlighting. Section 6.2.1.3 (p.196) has been updated with the following text: “This distribution gave the most optimistic predictions of TTP relative to the other distributions presented; therefore, the company presented a scenario analysis using a log-normal and an exponential distribution (see section 5.1.1.2).” The information in Table 6.1 pertains to the EAG base-case model, therefore no changes were made to this table.
Section 6.2.1, Table 6.1, Page 193, row 5.	The Company requests that the EAG review and update row 5 in Table 6.1.	The presentation of this issue in its current form within Table 6.1 suggests that the Company did not perform scenarios using data from the Arm C of the SEQUOIA trial, and that the EAG have resolved this issue through its own scenarios. The Company presented four scenarios using Arm C of the SEQUOIA trial (see Table 95 of CS), and hence this issue has not been solely resolved by the EAG but was also addressed by the Company within the original submission.	Thank you for highlighting. Section 6.2.1.3 (p.196) has been updated with the following text: “The company presented an independent visual assessment of arm A (untreated “unfit” cohort) and arm C (“high-risk” cohort) of KM data for TTP and PrePS. However, the EAG was not able to assess whether there was a clinically meaningful difference in the risk of progression across both populations from this analysis alone. Therefore, the EAG is still uncertain about the appropriateness of pooling data together these two populations. However, the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			acknowledges that due to the immaturity of the data, there may be additional issues and uncertainties to consider when comparing the KM data of the two subpopulations, specifically around mortality related outcomes. The company presented eight scenarios using the CS base-case model (see Section 5.1.1.2) to assess the cost-effectiveness evidence between for the "unfit" and the "high-risk" populations independently using a CMA approach, using a CUA approach with estimates of PFS from the ELEVATE-TN MAIC across both populations, and a CUA approach for the "high-risk" population using estimates from the ELEVATE-RR MAIC and the naïve comparison with Mato *et al*., (2018)." The information in Table 6.1 pertains primarily to the EAG base-case model, therefore no changes were made to this table.
Section 6.2.5, Page 207 and Figure 6.3: "Results from the DSA on the EAG base-case	The Company requests the text to be amended to:	The drug cost for zanubrutinib is fixed and should not be varied within the DSA. Hence should be removed from the text and the tornado (Figure 6.3).	The EAG have not commented on this except as a matter of judgement. While the company are offering a fixed price for zanubrutinib, it is important for the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
show that the parameters that had the largest impact on costs were: • The HR estimate for TTP • The HR estimate for PrePS • The drug acquisition costs for zanubrutinib, acalabrutinib and ibrutinib"	"Results from the DSA on the EAG base-case show that the parameters that had the largest impact on costs were: • The HR estimate for TTP • The HR estimate for PrePS • ~~The drug acquisition costs for zanubrutinib, acalabrutinib~~		decision-maker to understand what effect changes in the price of the drugs could have on conclusions. No changes to the report have been made.
Section 6.2.5, Page 207: "As shown in Figures 6.3 and 6.4 zanubrutinib was less costly when compared with acalabrutinib and was more effective, in terms of QALYs gained,	The Company requests the text to be amended to: "As shown in Figures 6.3 and 6.4 zanubrutinib was less costly when compared with acalabrutinib and	Contradicting sentences.	Thank you for highlighting. This sentence has been removed from the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
except when variations in the HR estimates for TTP and PrePS were applied. In these DSA results, zanubrutinib was less costly and less effective than acalabrutinib."	was more effective, in terms of QALYs gained, except when variations in the HR estimates for TTP and PrePS were applied. ~~In these DSA results, zanubrutinib was less costly and less effective than acalabrutinib."~~		
R/R CLL population			
Section 5.2.1.1, Page 178: **"**Differences in the PSA results are largely driven by the differences in drug acquisition costs associated with the three treatments."	The Company requests the text to be removed.	Incorrect statement. Drug costs are fixed and hence were not varied in the PSA. See Table 118 of CS.	Thank you for highlighting. This sentence has been removed from the EAG report.
Section 5.1.1.2, Page 166: "The following scenarios reduced the cost savings observed in the	The Company requests the text to be amended to: "The following scenarios reduced	The Company presented additional scenarios that have been omitted by the EAG from the report.	Thank you for highlighting. Section 5.2.1.2 (p.181) has been updated with the following text: "The list of parameters assumptions changed in the economic model include the following:

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
company's base-case analysis: • Discount rate • PFS endpoint (IRC-assessed) • PFS parametric survival model • OS parametric survival model • Excluding wastage • Using TTTD data for zanubrutinib and ibrutinib • A CUA using parameters from the MAIC in ELEVATE RR for acalabrutinib • A CUA using parameters from the MAIC in ASCEND for acalabrutinib"	the cost savings observed in the company's base-case analysis: • Discount rate • PFS endpoint (IRC-assessed) • PFS parametric survival model • OS parametric survival model • Excluding wastage • **Excluding AE costs** • Using TTTD data for zanubrutinib and ibrutinib • **Applying AE impact to QALYs**		• Discount rate • PFS endpoint (IRC-assessed) • PFS parametric survival model • OS parametric survival model • Excluding wastage • Excluding AE costs • Using TTTD data for zanubrutinib and ibrutinib • A CUA using parameters from the MAIC in ELEVATE RR for acalabrutinib • A CUA using parameters from the MAIC in ASCEND for acalabrutinib • Applying AE impact to QALYs • A CUA using ibrutinib ALPINE extrapolation • CUAs using parameters from the MAIC in ELEVATE RR for acalabrutinib (Model 1 and Model 2) • CUAs using parameters from the MAIC in ASCEND (Model 1 and Model 2) for acalabrutinib • CUA using Arm A and Arm C data separately applying HRs derived from ELEVATE-TN MAIC (Model 1 and Model 2) Mato et al. (2018) comparison and R/R data as a proxy."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	• A CUA using ibrutinib ALPINE extrapolation • CUAs using parameters from the MAIC in ELEVATE RR for acalabrutinib (Model 1 and Model 2) • CUAs using parameters from the MAIC in ASCEND (Model 1 and Model 2) for acalabrutinib • CUA using Arm A and Arm C data separately applying HRs derived from		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	ELEVATE-TN MAIC (Model 1 and Model 2), Mato et al. (2018) comparison and R/R data as a proxy."		
Section 5.2.1.2, Table 5.7, Page 182, table footnote: "*ICER for acalabrutinib versus zanubrutinib"	The Company requests the text to be amended to: "*Result represents a ICER in the SW quadrant of the incremental cost-effectiveness plane in which the cost-effectiveness threshold is reversed. An ICER greater than the willingness-to-pay (WTP) threshold of £20,000 - £30,000 is deemed cost-effective."	To aid interpretation of the SW ICER and to prevent confusion.	Thank you for highlighting. Section 5.2.1.2, Table 5.7 (p.184) has been updated with the following text: "*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib" to help aid the interpretation of the ICER.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.1.2, Table 5.8, Page 184, table footnote:	The Company requests to add the following into the footnote of Table 5.8: "*Result represents a ICER in the SW quadrant of the incremental cost-effectiveness plane in which the cost-effectiveness threshold is reversed. An ICER greater than the WTP threshold of £20,000 - £30,000 is deemed cost-effective."	To aid interpretation of the SW ICER and to prevent confusion.	Thank you for highlighting. Section 5.2.1.2, Table 5.8 (p.186) has been updated with the following text: "*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib" to help aid the interpretation of the ICER.
Section 5.2.1.2, Page 185: **"**The EAG notes an error in referencing of utility values provided by the company (see Section 4.4.8.2). If these values are not supported by the evidence, then there is	The Company requests the text to be removed.	The Company acknowledges a typographical error was made in the CS and utilities from appraisal TA561 were used in the economic model as opposed to utilities from appraisal TA516.	Thank you for highlighting. This sentence has been removed from the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the possibility that the CUA results (QALY difference) for the scenario analyses of the R/R CLL model presented by the company may not be correct”			
Section 5.2.4, Page 189: “The EAG explores the impact of alternative PFS and OS assumption, considering that the partitioned survival structure used for the R/R population is sensitive assumptions made about survival.”	The Company requests the text to be amended to: “The EAG **and the Company** explore**d** the impact of alternative PFS and OS assumption, considering that the partitioned survival structure used for the R/R population is sensitive assumptions made about survival.”	Scenarios which explored alternative PFS and OS curves were already included within the CS by the Company. The current statement is misleading and indicates that the Company did not provide such scenarios.	Thank you for highlighting. Section 5.2.4 (p.191) has been updated with the following text: “The EAG and the company explored the impact of alternative PFS and OS assumption, considering that the partitioned survival structure used for the R/R population is sensitive assumptions made about survival.”
Section 6.3.1.2, Page 219:	The Company requests the text to be amended to:	MAIC ASCEND Model 2 provides the most pessimistic estimates of comparative effectiveness for zanubrutinib versus acalabrutinib. It is important for	Thank you for highlighting. Section 6.2.1.2 (p.221) has been updated with the following text: “The EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"This approach applied the relative effectiveness estimates from the MAIC results of Model 2 comparing ALPINE and ASCEND on the OS and the PFS curves of zanubrutinib from ALPINE[13] to derive the OS and PFS for acalabrutinib."	"This approach applied the relative effectiveness estimates from the MAIC results of Model 2 comparing ALPINE and ASCEND on the OS and the PFS curves of zanubrutinib from ALPINE[13] to derive the OS and PFS for acalabrutinib. **The choice of MAIC ASCEND Model 2 is the most pessimistic option.**"	transparency to note that the EAG have selected results which will likely to lead more pessimistic cost-effectiveness estimates versus acalabrutinib in their base-case.	acknowledge that the choice of MAIC ASCEND Model 2 was the least favourable option for zanubrutinib."
Section 6.3.1.3, Table 6.10, Page 220, row 4.	The Company requests that the EAG review and update row 4 in Table 6.10 to acknowledge that PFS and OS survival scenarios were also performed by the Company.	The presentation of this issue within Table 6.10 suggests that the Company did not perform scenarios using alternative PFS and OS distributions. The Company presented two scenarios (see Table 124 of CS), and hence this issue has not been solely resolved by the EAG but was also addressed by the Company within the original submission.	Thank you for highlighting. Section 6.3.1.3 (p.223) has been updated with the following text: "The scenario analysis presented by the company explored the Gompertz distribution as an alternative to model PFS and the Exponential distribution as an alternative to model OS." The information in Table 6.10 pertains primarily to the EAG base-case model,

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			therefore no changes were made to this table.
Section 6.3.3.1, Table 6.11, Page 224, table footnote.	The Company requests the following footnote is added into Table 6.11: "*Result represents a ICER in the SW quadrant of the incremental cost-effectiveness plane in which the cost-effectiveness threshold is reversed. A ICER greater than the WTP threshold of £20,000 - £30,000 is deemed cost-effective."	To aid interpretation of the SW ICER and to prevent confusion.	Thank you for highlighting. Section 6.3.3.1, Table 6.11 (p.226) has been updated with the following text: "*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib."
Section 6.3.3.1, Table 6.14, Page 226, table footnote.	The Company requests the following footnote is added into Table 6.12:	To aid interpretation of the SW ICER and to prevent confusion.	Thank you for highlighting. Section 6.3.3.1, Table 6.14 (p.228) has been updated with the following text: "*ICER for acalabrutinib versus zanubrutinib as acalabrutinib was more

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"*Result represents a ICER in the SW quadrant of the incremental cost-effectiveness plane in which the cost-effectiveness threshold is reversed. An ICER greater than the WTP threshold of £20,000 - £30,000 is deemed cost-effective."		costly and more effective than zanubrutinib."

Issue 6 Factually inaccurate statements and clarity of language

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1.1, Page 48, Table 3.2, Row 4 "In the absence of head-to-head trial evidence of zanubrutinib versus all UK relevant comparators, an indirect treatment	The Company requests that the justifications in these columns are updated.	The justifications of the descriptions of the inclusion criteria are not relevant and should be updated accordingly. The justification for these comparators is included in Page 14 of the Draft Scope.	Thank you for highlighting. Section 3.1.1, Table 3.2 (p.48) the heading has been changed to EAG comment instead of justification.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
comparison was undertaken." **Section 3.1.1, Page 48, Table 3.2, Row 4** "RCTs represent the gold standard for assessing intervention effectiveness and the main evidence is based on this study design."			
Section 3.1.4, Page 51 "The process for undertaking quality assessment was not reported in the CS.15 As such, the EAG cannot comment on the appropriateness of the methods used to appraise study quality in the SLR." "The quality assessments for each domain in the other trials forming part of the CS evidence synthesis were incomplete."	The Company requests that these sections of text are removed.	Incorrect statements. The critical appraisal of the SEQUOIA and ALPINE trials was performed using the criteria for the assessment of risk of bias and generalisability listed in Section 2.5.2. of the NICE STA user guide.[31,32] This was noted by the Company in response to EAG clarification question A19. The quality assessments of other	Thank you for highlighting. The EAG appreciates that further details of how the SEQUOIA and ALPINE trials were critically appraised and updated critical appraisals for these trials with further justifications for assessments were provided within the company's response to the clarification letter. This is stated in Sections 3.2.1.1 and 3.2.2.1 of the EAG Report. Section 3.1.4 (p.51) the following text has been updated: "The quality assessments for SEQUOIA and ALPINE are critiqued by the EAG in Sections 3.2.1.1 and 3.2.2.1 respectively. The quality assessments for the other trials forming part of the CS evidence synthesis lacked detail in supporting statements for individual domain assessments. The company only provided additional supporting evidence to their risk of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		trials (beyond SEQUOIA and ALPINE) are included within Appendix D of the CS.	bias judgements in the trials that included zanubrutinib." Furthermore, company's response to the clarification letter does not explain the method of critical appraisal (e.g., whether there were two independent reviewers undertaking critical appraisal, as is considered gold standard). Consequently, the EAG is unable to comment on the appropriateness of the methodology used by the company. Regarding the presentation of the critical appraisal of the included studies within the SLR, the EAG report states that these were contained within the CS but were considered "incomplete" because the assessments presented in Appendix D, Table 19 often do not present sufficient justification for the assessments. For clarity, in Section 3.1.4 (p. 51) the EAG have rephrased to the text to: "The quality appraisal in the other trials forming part of the CS evidence synthesis lacked detail in supporting statements for individual domain assessments."
Section 3.3, Page 85, Table 3.20, Row 5-7: The sample size reported in the 'Sample size' column corresponds to the whole treatment arm	The Company requests replacing these sample sizes with those which correspond to the subgroup reported in the '17p deletion and/or TP53 mutation' column.	Subgroup sample sizes should be reported to avoid confusion.	Thank you for highlighting. Section 3.3, Table 3.20 (p.85) has been updated with the proportion of patients with 17p deletion and/or TP53 mutations for each of the analyses.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
rather than subgroup specified.			
Section 4.2.1, Page 123, Table 4.5, Row 8: "No targeted reviews were performed for HRQoL, cost and resource use data."	The Company requests that this statement is removed.	As highlighted in Appendix D, supplementary searches of "grey" literature were performed through the NICE and SMC websites which identified HRQoL, cost and resource use data.	Thank you for highlighting. The statement has been removed as recommended by the company. Section 4.2.1, Table 4.5 (p.124) has been updated with the following text "The company applied a quality of life and Economic filter to these search results. In addition, the company searched NHS EED and HTA databases."
Section 4.3.6.1.1, Page 129: "An assessment of KM data between arm A and arm C was not presented in the CS"	The Company requests that this statement is removed.	The Company presented separate KM for ICR-assessed TTP data for Arm A and Arm C in Appendix M of the CS, and within Section B2a. Specifically, the KM data for Arm A is presented in Figure 5 of Appendix M and the KM data for Arm C is presented in Figure 8 of Appendix M. The figures demonstrate that the outcomes following	Thank you for highlighting. The EAG acknowledges that the company presented a visual assessment for the KM data for Arm A and Arm C Section 4.3.6.1.1 (p.130) has been updated with the following text: "[redacted]. The company provided a visual assessment of TTP data for arm A and arm C independently in appendix M; however, this analysis did not compare the two arms together. The EAG considers that a statistical assessment of the progression hazards between the "unfit" (arm A) and "high-risk" (arm C) populations should have been provided using KM TTP data from both arms of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		treatment with zanubrutinib is consistent across both treatment arms. Furthermore, the appropriateness of pooling the data was validated by experts in attendance at an advisory board organised by the Company.	SEQUOIA, to better justify pooling the data together for use in the model. Furthermore, a statistical assessment of SEQUOIA outcomes across arm A and arm C was feasible and is likely to be informative from a clinical perspective." The EAG acknowledges the visual assessment of the KM curves but considers that a statistical assessment of the KM data for TTP between both populations was feasible and necessary to justify the appropriateness of pooling this data together and using it in the model. Section 4.3.6.1.1 (p.130) has been updated with the following text: "In the absence of a statistical analysis between arm A and arm C, it is uncertain to the EAG whether data from the SEQUOIA trial suggested significant differences in disease progression across untreated CLL patients with del17p (arm A) versus patients without del17p (arm C). A scenario analysis was presented using parametric survival curves from data on arm A and arm C independently. The AIC estimates reported in Table 4.6 present small differences across the parametric distributions, which makes the selection of a model primarily dependent on external evidence."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.6.1.1, Page 129: [redacted]"	The Company requests that this statement is removed.	Clinicians at the advisory board did not suggest that a statistical and graphical assessment of the pooled data would have been informative and the Company does not believe this can be inferred from the advisory board report provided.	Thank you for highlighting, the EAG considers this is a misunderstanding, the statement cited is not meant to suggest a statistical and graphical assessment. The EAG interprets the comment by the clinicians as a suggestion of the informative potential of a comparison between Arm A and Arm C. Section 4.3.6.1.1 (p.130) has been updated with the following text "[redacted]. The company provided a visual assessment of TTP data for arm A and arm C independently in appendix M; however, this analysis did not compare the two arms together. The EAG considers that a statistical assessment of the progression hazards between the "unfit" (arm A) and "high-risk" (arm C) populations should have been provided using KM TTP data from both arms of SEQUOIA, to better justify pooling the data together for use in the model. Furthermore, a statistical assessment of SEQUOIA outcomes across arm A and arm C was feasible and is likely to be informative from a clinical perspective." The statement [redacted]" has been deleted from the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.6.1.1, Page 129: "However, the process of selecting the parametric distributions used in these scenarios was not detailed in the submission."	The Company requests that this statement is removed.	The Company presented the selection process for the survival distributions of Arm A and Arm C in Appendix M of the CS.	Thank you for highlighting. This sentence has been removed from the EAG report.
Section 4.3.6.1.2, Page 131: "The "~60% progression free patients at 8 years" benchmark, reported in the CS (page 182),[5] as obtained from the advisory board, appears to refer to TTP which makes the latter comparison the company makes with modelled PFS predictions potentially misleading."	The Company requests that this statement is revised.	Incorrect statement. Expert opinion gathered that the advisory board refers to the RESONATE-2 trial and the proportion of patients who remain event free in the PFS endpoint. Hence the ~60% progression free refers to PFS and not TTP. Hence the modelled PFS predictions are not misleading and instead are aligned to the long-term data from RESONATE-2.	Thank you for highlighting. This sentence has been removed from the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.6.2.1, Page 133: "The MAIC relies on data from arm A and arm C of SEQUOIA being pooled together to generate the evidence for zanubrutinib, [redacted][14] "	The Company requests the text to be amended to: "The MAIC relies on data from arm A and arm C of SEQUOIA being pooled together to generate the evidence for zanubrutinib, [redacted]"	Advisors at the advisory board did not raise concerns about the pooling of the sub-population and the Company does not believe this can be inferred from the advisory board report provided. Instead, [redacted].	Thank you for highlighting. Section 4.3.6.2.1 (p.134) has been updated with the following text: "The MAIC relies on data from arm A and arm C of SEQUOIA being pooled together to generate the evidence for zanubrutinib, [redacted]"
Section 4.3.6.2.2, Page 134: **"**However, the determinant factor for R/R CLL patient data to be a suitable proxy for the "high-risk" untreated population is the proportion of R/R CLL patients with del17p and/or TP53 mutation. For the	The Company requests the text to be amended to: **"**However, the determinant factor for R/R CLL patient data to be a suitable proxy for the "high-risk" untreated population is the proportion of R/R CLL patients with del17p and/or TP53 mutation. **For the ELEVATE-RR trial, 45.3% of patients had a del17p mutation and 37.4%**	The original text lacks clarity.	Thank you for highlighting. Section 4.3.6.2.2 (p.136) has been updated with the following text: "For the ELEVATE-RR trial, 45.3% of patients had a del17p mutation and 37.4% of patients had a TP53 mutation, while for the ASCEND trial it was 18.1% and 25.2%, respectively."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ELEVATE-RR trial, this was 45.3%, while for the ASCEND trial it was 18.1%, which in both cases is still less than 50%. This makes data from these trials potentially unsuitable as a proxy for "high-risk" untreated CLL."	**of patients had a TP53 mutation, while for the ASCEND trial it was 18.1% and 25.2%, respectively**."		
Section 6.2.1.3, Page 194 **"**As an independent assessment of KM data was not presented for arm A and arm C as part of the SEQUOIA trial results,[10] the EAG is unsure about the appropriateness of pooling this data together to represent the untreated CLL population."	The Company requests the text to be removed.	KM data and an accompanying interpretation about the consistency of outcomes for zanubrutinib from both arm A and Arm C of the SEQUOIA trial is presented within Section B2a of the CS, and hence it is incorrect to state that assessment of the KM data was not performed. Furthermore, the appropriateness of pooling Arm A and Arm C was validated by	Thank you for highlighting. The EAG acknowledges the information in the EAG report was unclear. Section 6.2.1.3 (p.196) has been updated with the following text: "The company presented an independent visual assessment of arm A (untreated "unfit" cohort) and arm C ("high-risk" cohort) of KM data for TTP and PrePS. However, the EAG was not able to assess whether there was a clinically meaningful difference in the risk of progression across both populations from this presentation of the data. Therefore, the EAG is still uncertain about the appropriateness of pooling data together these two populations. However, the EAG acknowledges that due to the immaturity of the data, there may be additional issues and uncertainties to consider when comparing the KM data of the two subpopulations, specifically around mortality related outcomes."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		experts in attendance at the advisory board meeting organised by the Company.	The visual analysis performed using KM data in appendix M was considered informative, but not sufficient to assess a whether there was a clinically meaningful difference between Arm A and Arm C. The EAG considers this analysis is feasible and has the potential of being informative.

Issue 7 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1.5, Page 64: "Participant-reported outcomes (PROs) were only assessed in SEQUOIA Cohort 1 (CS, Table 10).[4]" "The LS difference between the two arms in pain was significant at Week 12 ([redacted]) but not at Week 24 (CS, Table 10).[4]"	The Company requests that the EAG update the text as follows: "Participant-reported outcomes (PROs) were only assessed in SEQUOIA Cohort 1 (CS, Table ~~10~~ **24**).[4]" The LS difference between the two arms in pain was significant at Week 12 ([redacted]) but not at Week 24 (CS, Table ~~10~~ **24**)	Wrong cross reference to CS.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 3.3.1.1, Page 87: "The trial characteristics and eligibility criteria for the two studies included in the MAIC	The Company requests that the EAG update the text as follows: ""The trial characteristics and eligibility criteria for the two studies	Incorrect table reference.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
analysis (SEQUOIA, ELEVATE-TN) is provided in Tables 11 and 12 in the CS."	included in the MAIC analysis (SEQUOIA, ELEVATE-TN) is provided in Table 44 in the CS."		
Section 3.3.2.1, Page 95: "The study characteristics and eligibility criteria for the three studies included in MAIC analyses (ALPINE, ELEVATE-RR and ASCEND) are provided in the CS (Tables 11 and 12)."	The Company requests that the EAG update the text as follows: "The study characteristics and eligibility criteria for the three studies included in MAIC analyses (ALPINE, ELEVATE-RR and ASCEND) are provided in the CS (Tables **49** and **55**)."	Incorrect table reference.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 3.3.2.1, Page 95: "The unadjusted population characteristics of the acalabrutinib monotherapy arms in ELEVATE-RR and ASCEND compared with the population in the zanubrutinib arm in ALPINE are presented in CS Tables 49 and 56, respectively."	The Company requests that the EAG update the text as follows: "The unadjusted population characteristics of the acalabrutinib monotherapy arms in ELEVATE-RR and ASCEND compared with the population in the zanubrutinib arm in ALPINE are presented in CS Tables **50** and 56, respectively."	Incorrect table reference.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 4.3.4, Page 127: "Ibrutinib was used as a comparator for the untreated CLL "high-risk" subgroup and, in current practice, is administered orally once daily as 400 mg per	The Company requests that the EAG update the text as follows: "Ibrutinib was used as a comparator for the untreated CLL "high-risk" subgroup and, in current practice, is administered orally once daily as	Typographical error. As per the Ibrutinib Summary of Product Characteristics (SmPC), the dosage strength of ibrutinib is 420 mg.[26]	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
administration until either disease progression or death.”	**420 mg** per administration until either disease progression or death.”		
Section 4.3.6.1.1, Page 128: “Moreover, the company decided to align the distribution functions for TTP and PrePS to provide a better representation of PPS.”	The Company requests that the EAG update the text as follows: “Moreover, the company decided to align the distribution functions for TTP and PrePS to provide a better representation of **PFS**.”	Typographical error.	Thank you for highlighting. The EAG has updated the report with the company’s suggested edit.
Section 5.1.1.2, Page 166: Throughout section	The Company requests that the EAG update full stops separating numbers with commas. For example, “[redacted]” to be replaced with “[redacted]”	Typographical error.	Thank you for highlighting. The EAG has updated the report with the company’s suggested edit.
Section 4.4.6, Page 154: “The company did not explore alternative approaches for acalabrutinib due to the absence of corresponding TTP data.”	The Company requests that text is updated to: “The company did not explore alternative approaches for acalabrutinib due to the absence of corresponding **TTD** data.”	Typographical error.	Thank you for highlighting. The acronym used for time to treatment discontinuation is TTTD, the text was updated accordingly.
Section 5.1.1.2, Page 166: “incrmental"	The Company requests that text is updated to:	Typographical error.	Thank you for highlighting.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"incremental"		The EAG has updated the report with the company's suggested edit.
Section 5.1.2, **Page 175:** In a further scenario analysis using a cost-utility approach in the "unfit" population, zanubrutinib was demonstrated less costly ([redacted]) and more effective ([redacted] QALY gain) and so dominated acalabrutinib.	The Company requests that text is updated to: "In a further scenario analysis using a cost-utility approach in the "unfit" population, zanubrutinib was ~~demonstrated less costly (~~ ~~£313,528)~~ **associated with a cost saving of** [redacted] and was more effective ([redacted] QALY gain) and so dominated acalabrutinib."	Clarity to align with how the text in the rest of the paragraph is presented.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 5.2.1.2, Page 179: "The results showed cost savings ranging between [redacted] and [redacted] for zanubrutinib compared with ibrutinib and cost savings ranging between [redacted] and [redacted] for zanubrutinib compared with acalabrutinib."	The Company requests that text is updated to: "The results showed cost savings ranging between [redacted] and [redacted] for zanubrutinib compared with ibrutinib and cost savings ranging between [redacted] and [redacted] for zanubrutinib compared with acalabrutinib."	Incorrect value reported.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 5.2.1.2, Table 5.8, Page 184: "1,674,256.4"	The Company requests the text to be updated to: "1,674,256.4*"	Footnote '*' missing from SW ICERs.	Thank you for highlighting. Section 5.2.1.2, Table 5.8 (p.186) the following footnote has been included: "*ICER for

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"341,061.85"	"341,061.85*"		acalabrutinib versus zanubrutinib as acalabrutinib was more costly and more effective than zanubrutinib."
Section 6.2.1, Table 6.1, Page 193, row 2, column 7: "Utility data was nor recorded for Cohort 2 of SEQUOIA,[10] therefore differences HRQoL across patients with del17p and/or TP53 mutation are unknown."	The Company requests that text is updated to: "Utility data was **not** recorded for Cohort 2 of SEQUOIA,[10] therefore differences HRQoL across patients with del17p and/or TP53 mutation are unknown."	Typographical error.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.2.4.1, Page 199: "presentes"	The Company requests that text is updated to: "presents"	Typographical error.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.2.4.1, Table 6.6, Page 203, Scenario 3, Column 5: [redacted]	The Company requests that text is updated to: [redacted]	Incorrect result reported.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.2.4.1, Table 6.8, Page 204, Subgroup 2, Column 4: [redacted]	The Company requests that text is updated to: [redacted]	Incorrect result reported.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.2.4.1, Table 6.8, Page 204, Subgroup 2, Column 4-6: [redacted]	The Company requests that text is updated to: [redacted]	Incorrect result reported.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.2.6, Page 214: "Ibrutinib was included as a comparator for untreated CLL ("unfit" and "high-risk") but in practice it is only provided to those who are "high risk" and was administered orally once daily at 400 mg per administration."	The Company requests that text is updated to: "Ibrutinib was included as a comparator for untreated CLL ("unfit" and "high-risk") but in practice it is only provided to those who are "high-risk" and was administered orally once daily at **420 mg** per administration."	Typographical error. As per the Ibrutinib SmPC, the dosage strength of ibrutinib is 420 mg.[26]	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.3.3.1, Page 226, Table 6.14, Scenario 2, Column 6: "£287,979*"	The Company requests that text is updated to: "£287,909*"	Incorrect result reported.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.3.3.1, Page 226, Table 6.14, Scenario 3, Column 4: [redacted]	The Company requests that text is updated to: [redacted]	Incorrect result reported.	Thank you for highlighting. The EAG has updated the report with the company's suggested edit.
Section 6.3.3.1, Page 226, Table 6.14, Scenario 3, Column 6: "£339,910"	The Company requests that text is updated to: "£339,746"	Incorrect result reported.	Thank you for highlighting.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			The EAG has updated the report with the company's suggested edit.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 17 May**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted], [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	BeiGene UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	Submitting Company
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

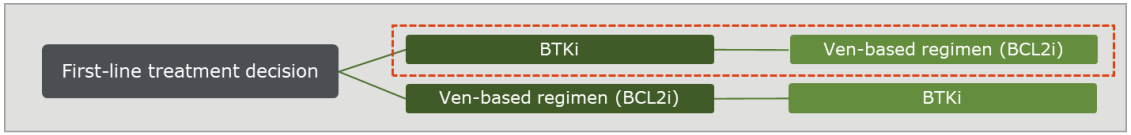
Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL	No	The Company does not consider venetoclax-rituximab to be a comparator to zanubrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) and so believe that the exclusion of venetoclax-rituximab is justified. A 'sequencing' approach is recommended in the 2022 British Society for Haematology (BSH) guidelines when selecting the optimal strategy for patients who have relapsed following treatment with front-line targeted agents.[1] Treatment sequencing suggests that the optimal treatment following progression varies depending on the front-line therapy (as per Figure 1 below): • For patients progressing following front-line treatment with a Bruton tyrosine kinase inhibitor (BTKi), a B-cell lymphoma 2 inhibitor (BCL2i) regimen is recommended. • For patients progressing following front-line treatment with a BCL2i, a BTKi regimen is recommended.

Figure 1: Treatment decision as per BSH guidelines



The introduction of zanubrutinib will 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 patients with R/R CLL. Whilst venetoclax-rituximab is recommended by the National Institute for Health and Care Excellence (NICE) for patients with R/R CLL irrespective of which prior therapy was received, as noted in the 2022 BSH guidelines there is a distinct lack of data on rechallenging patients with a venetoclax-based regimen.[1] Venetoclax-rituximab is primarily used in patients previously treated with a BTKi.[2]

The Company acknowledges that a small proportion of patients who are treated with front-line chemo-immunotherapy (CIT) may receive second-line venetoclax-rituximab. However, the introduction of targeted pathway inhibitors has represented a paradigm shift in front-line treatment, challenging the role of CIT.[1] This was confirmed by UK experts at an advisory board (3rd November 2022) who emphasised that CIT usage has declined in the first-line setting since the availability of targeted therapies. This conclusion was also reiterated by the submitting Company of NICE ID 3860, who noted that *'the role of CIT in first-line treatment has diminished following the approval of targeted pathway inhibitors in recent years'*.[3,4] As the use of CIT continues to decrease, the pathway for patients will continue moving towards a BTKI/BCL2i sequencing approach, as recommended in the BSH guidelines.[1]

In addition, based on UK prescribing data, only [redacted]% of patients received second-line treatment with venetoclax-rituximab, whereas [redacted]% of patients received second-line treatment with a BTKi. This is likely due to the intensive dosing regimen of venetoclax-rituximab and the associated risk of tumour lysis syndrome. In comparison, [redacted] of patients received third-line treatment with a venetoclax-based therapy, whereas only [redacted]%

		of patients received third-line treatment with a BTKi. This indicates that the treatment sequencing algorithm in patients not treated with a BTKi in the first-line is to receive a BTKi in second-line and a BCL2i in third-line. Patients eligible for zanubrutinib are those who have not previously received treatment with a BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib.[5] This was confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[3] Furthermore, feedback gathered from UK experts at an advisory board (3rd November 2022) conducted by the Company supported the sequencing concept and the positioning of zanubrutinib as an alternative BTKi treatment option in this patient population.[6] The Company would also like to reemphasise that the network meta-analysis (NMA) analysis (versus venetoclax-rituximab) conducted by the Evidence Assessment Group (EAG) is subject to substantial uncertainty as noted in the Company response to the EAR and in the limitations noted by the EAG regarding their methodology. As such, the NMA analysis is unsuitable for use to inform decision-making.
Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL	No	The Company conducted a robust clinical systematic literature review (SLR) using the Embase interface (via Embase.com), an interface which is commonly used in conducting SLRs forming evidence submissions to NICE and considered to be a core database for literature searching in the NICE literature searching and evidence submission guidelines.[7–11] The Embase interface searches Embase, EMBASE classic and MEDLINE databases simultaneously using one search strategy and as such, there is no need to use separate search strategies to search the individual databases. The search terms are translatable to other interfaces, such as Ovid, meaning that the EAG would be able to test the search strategies within the databases they have access to, if required. All relevant literature for previously untreated and R/R CLL were retrieved through the appropriate search terms. The EAG were not able to identify additional publications that were missed within the database searches or note any additional publications that would be relevant to decision making. Follow-up interviews with two leading UK clinical experts confirmed that all key studies relevant for decision-making were captured in the SLR.[12]

		When comparing to the ibrutinib-venetoclax appraisal (TA10746), no additional publications were identified in this appraisal compared to the Company's appraisal. The literature used to inform the matching adjusted indirect comparison (MAIC) conducted versus acalabrutinib (ELEVATE-TN) in TA10746 was in line with the literature the Company used for their MAIC analysis versus acalabrutinib as reported in the CS.[13] Both appraisals have used Sharman *et al.* (2020) as a data source for ELEVATE-TN.[14] Relevant conference and abstract proceedings were captured in the SLR, and the amendments made to the Scottish Intercollegiate Guidelines Network (SIGN) filters would not impact the ability of the filter to capture relevant studies as the edits made were to widen the filters to capture conference abstracts and proceedings (which the filter previously omitted). Both branded and generic drug names were included in the search terms for the intervention and comparator. Exploded search terms were used for the generic drug names meaning any words or phrases associated with the names would have been captured. Therefore, it is highly unlikely that any key publications were missed. Additionally, grey literature searches or 'hand-searches' were conducted by the Company to identify any additional conference abstracts that the Embase interface may have missed – these searches did not identify any additional publications. The Company would also like to outline that conference abstracts would unlikely contain sufficient information to impact decision-making. As MAICs are required to adjust for heterogeneity, data on aggregate cohort characteristics would be required, which are rarely reported within a conference abstract. Whilst the Company appreciates that the SLR was now conducted 9 months ago given the timelines associated with the NICE process, the Company would like to reiterate that the SLR was conducted in line with NICE requirements and was conducted within 6 months of submission as per the NICE methods guide.[15] The EAG recognised that this is a **common** concern of the Health Technology Assessment (HTA) process and its variable timelines, therefore reducing the severity of the concern over the timelines of the Company's SLR. In addition, the Company's medical team regularly keep up to date with new publications that could be relevant for use in the submission and no additional publications have been identified by them.

		The Company conducted additional searches in nonbibliographic databases including the NICE and Scottish Medicine Consortium (SMC) websites using alternative spelling and search terms without identifying any additional key publications that would be relevant to the appraisal. The methods used by the Company for the SLR are aligned with previous NICE appraisals and follow the NICE methods guide.[15] The Company believes that the EAG's concern over the methods have **no** material impact on decision-making ability.
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison	No	**<u>Trial designs and eligibility</u>** The Company agrees with the EAG's conclusion that the definition of patient fitness is non-binary, driven by mainly patient characteristics as opposed to treatment eligibility (as confirmed by UK clinical experts [please refer to section below Table 1]).[12] In addition, clinical experts confirmed that the definition of 'fitness' is subjective and becoming less relevant in driving treatment decisions given the declining usage of CIT. Hence, it is important to compare trial design, and patient eligibility across relevant front-line trials in CLL to demonstrate that SEQUOIA is appropriate for decision-making in previously untreated patients with CLL. Key eligibility criteria and patient characteristics of SEQUOIA, ELEVATE-TN and CLL10 are presented in Table 1. The SEQUOIA trial is overall more akin to the eligibility criteria and patients characteristics for the ELEVATE-TN trial which was deemed representative of the previously untreated "unfit" patients with CLL by NICE.[16,17] In comparison, there is a difference in the key eligibility criteria for CLL10 which was deemed representative of the previously untreated "fit" patients with CLL by NICE.[18] The key differences between the inclusion criteria of the CLL10 trial and the SEQUOIA trial are age, Cumulative Illness Rating Scale (CIRS) score and creatine clearance level. The only key difference between the eligibility criteria of the SEQUOIA trial and the ELEVATE-TN trial is that patients in the SEQUOIA trial were eligible for treatment with bendamustine-rituximab whereas patients in the ELEVATE-TN trial were not eligible for treatment with bendamustine-rituximab. Bendamustine-rituximab was used as a comparator in the SEQUOIA trial because at the time of study design, the standard front-

line treatment in patients without 17p deletion or TP53 mutation was CIT. Bendamustine-rituximab was a commonly used standard treatment option for front-line "unfit" CLL patients without 17p deletion in the countries in which the trial was to be conducted.[19,20] In the UK, bendamustine-rituximab was recommended as an alternative treatment option for less "fit" patients with CLL by the BSH in their 2018 guidelines,[21] but has since been removed in the most recent 2022 guidelines following the introduction of targeted therapies. The choice of bendamustine-rituximab was agreed upon as a globally acceptable comparator with regulatory authorities, including the Food and Drug Administration (FDA) and European Medicines Association (EMA).

The EAG acknowledge that the SEQUOIA trial recruited patients who were not "fit" for intensive CIT (e.g. fludarabine-cyclophosphamide-rituximab), however were suitable to receive treatment with bendamustine-rituximab. Therefore, the SEQUOIA trial bridges the gap between the CLL10 trial (suitable for either fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab) and the ELEVATE-TN trial (not suitable for either fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab). This was supported by UK clinical experts who described patients in ELEVATE-TN and SEQUOIA as 'no go patients' and 'slow go patients' for CIT, respectively.[12] This overlap in eligibility criteria, allows clinical data from SEQUOIA to be comparable to ELEVATE-TN, to allow for a robust MAIC of zanubrutinib versus acalabrutinib in the "unfit" patient population. At the same time, the fact that patients could tolerate bendamustine-rituximab in SEQUOIA means there is also overlap with patients in the CLL10 trial. Overall the Company consider that the SEQUOIA trial is appropriate for decision-making for the previously untreated CLL patient population irrespective of fitness levels.

Table 1: Key inclusion criteria of CLL trials

Characteristic	CLL10[18]	SEQUOIA (Cohort 1)[17]	ELEVATE-TN[16]
Interventions	FCR (n=282) BR (n=279)	Zanubrutinib (n=241) BR (n=238)	Acalabrutinib-obinutuzumab (n=179) Acalabrutinib (n=179) Chlorambucil-obinutuzumab (n=177)
Trial design	Phase III, open-label	Phase III, open-label	Phase III, open-label

Age	Aged ≥18	Aged ≥65 years, or 18 - 64 years if presenting with more severe disease as defined by CIRS score, creatinine clearance or infection history	Aged ≥65 years, or 18 - 64 years if presenting with more severe disease as defined by CIRS score and creatinine clearance
FCR/BR eligibility	FCR, BR eligible	FCR ineligible, BR eligible	FCR, BR ineligible
Key inclusion criteria	Patients must meet all criteria: **Age:** ≥18 years **CIRS:** ≤6 **Creatinine clearance:** ≥70 mL/min **Other:** -	Patients must meet at least **one** of the following criteria: **Age:** ≥65 years **CIRS:** >6 **Creatinine clearance:** <70 mL/min **Other:** History of severe or frequent infections	Patients must meet at least **one** of the following criteria: **Age:** ≥65 years **CIRS:** >6 **Creatinine clearance:** <70 mL/min **Other:** -
ECOG PS	0 – 2	0 – 2	0 - 2
Key exclusion criteria	Detection of del(17p)	Detection of del(17p)	-

BR – Bendamustine-rituximab; CIRS – Cumulative Illness Rating Scale; del(17P) – Deletion of the short arm chromosome 17; ECOG PS - Eastern Cooperative Oncology Group Performance Score; FCR – Fludarabine-cyclophosphamide-rituximab; min – Minute; mL – Millilitre.

Clinical validation

Follow-up interviews with two leading UK clinical experts practicing in CLL held via a teleconference (27th April 2023) conducted by the Company confirmed that in current clinical practice, BR would not be considered as an appropriate treatment option for the patient population of the SEQUOIA trial based on current guidelines.[12] They stated that the comparator arm is irrelevant to decision-making given that the treatment guidelines have changed since enrolment for the SEQUOIA trial following the introduction of newer targeted therapies (first patient randomised in SEQUOIA on 31th October 2017 whereas

		BR was removed as a recommendation for less "fit" patients with CLL from the UK BSH guidelines in 2022).[1,17] They noted that consideration of clinical characteristics is more important in determining fitness, with both clinicians agreeing that the inclusion criteria of the SEQUOIA trial and the ELEVATE-TN trial are aligned. Moreover, the clinical experts highlighted that treatment eligibility should not be used to define fitness of patients as eligibility for treatments changes over time based on treatment guidelines and there is currently crossover in eligibility for treatments based on previous definitions. They also noted that, given that most patients can tolerate targeted therapies now (whether above or below 65 years old), classifying patients by 'fitness' status is becoming less relevant in driving treatment decisions. **Regulatory support** The European approval of zanubrutinib by the EMA confirms the applicability of the SEQUOIA patient population to the previously untreated "unfit" population: *"Despite inclusion exclusion criteria of study 304 [SEQUOIA] in the frontline setting clearly indicate that patients should have been unsuitable for treatment [with] chemoimmunotherapy (FCR), study 305 [ALPINE] showed noninferiority and superiority (based on INV assessment) against ibrutinib in the R/R setting. Having in mind that ibrutinib is also approved in 1L, and recommended in both fit and unfit patients, it seems justified to extrapolate the use of zanubrutinib to 1L fit patients. Thus, despite the limitations of study 304 and the comparison against BR in an elderly and unfit population, the totality of evidence supports the use of zanubrutinib in both fit and unfit patients."*[22]
Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL **Issue 6:** Use of a cost-minimisation analysis as the	No	A comprehensive SLR was conducted to identify the most appropriate evidence to inform the efficacy of zanubrutinib, acalabrutinib and ibrutinib. Three MAICs were conducted comparing zanubrutinib with acalabrutinib in patients with previously untreated and R/R CLL. The MAICs were conducted in line with NICE recommended methodology and made best use of the available evidence for zanubrutinib and acalabrutinib.[23] Whilst the MAICs did not demonstrate a statistically significant difference in progression-free survival (PFS), all MAICs demonstrated a

company's base case in untreated CLL and R/R CLL **Issue 9:** Uncertainty in untreated "high-risk" CLL subgroup		numerical improvement in PFS for zanubrutinib compared to acalabrutinib. To alleviate uncertainty in the MAIC estimates and align with previous appraisals in CLL, the Company took the conservative approach to assume equal efficacy and safety within a cost-minimisation analysis (CMA) approach despite demonstrating improved PFS in all MAIC models.[16] There is a paucity of evidence specifically reported in patients with 17p deletion and/or TP53 mutation for alternative BTKis and no studies were identified in the SLR which reported outcomes and baseline characteristics for this patient population. Cohort 2 of SEQUOIA is among the largest bodies of prospective evidence collected specifically for patients with a 17p deletion and demonstrated consistent outcomes to treatment with zanubrutinib in patients without 17p deletion (comparable to outcomes of arm A in Cohort 1). The issue of a lack of data in "high-risk" CLL has been evident across several previous appraisals in patients with previously untreated CLL. In NICE TA689 and TA429, it was agreed that data from the R/R setting is an appropriate proxy to inform the clinical effectiveness of two BTKis (acalabrutinib and ibrutinib) in patients with previously untreated "high-risk" population.[24,25] The ALPINE trial showed clinical superiority of zanubrutinib over ibrutinib in the R/R setting, and a statistically significant improvement in PFS versus ibrutinib in patients with "high-risk" R/R CLL. Since the ELEVATE-RR trial showed acalabrutinib to be non-inferior to ibrutinib, it follows that it is plausible to assume that zanubrutinib is at least clinically equivalent to acalabrutinib and ibrutinib. The assumption of equal efficacy in patients with previously untreated "high-risk" CLL was validated with UK clinical experts in attendance at an advisory board (3rd November 2022) and follow-up interviews with two UK clinical experts who deemed the conclusion that the treatment effect of zanubrutinib is at least equivalent compared to alternative BTKis as clinically plausible.[6,12] The Company have also presented additional analyses to support the efficacy of zanubrutinib in patients with previously untreated "high-risk" CLL. This included a MAIC comparing zanubrutinib with acalabrutinib in a previously untreated (unfit and "high-risk") patients (using ELEVATE-TN) and a MAIC comparing zanubrutinib with acalabrutinib in

		patients with “high-risk” R/R CLL (using ELEVATE-RR), both demonstrating that PFS and overall survival (OS) between acalabrutinib and zanubrutinib is not statistically significantly different, irrespective of patient’s mutational status. Furthermore, a naïve comparison was conducted with ibrutinib using Mato et al (2018), which was the only ibrutinib study identified for the “high-risk” population during the clinical SLR. The naïve comparison demonstrated that there was no statistically significant difference in PFS between zanubrutinib and ibrutinib. However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib, in favour of zanubrutinib. Interviews with two UK clinical experts confirmed that the Mato et al publication provides useful evidence for ibrutinib to use in a naïve comparison and that this should be sufficient to demonstrate that there is at least equal efficacy between zanubrutinib and other BTKis in patients with previously untreated “high-risk” CLL.[12] As recommended in the NICE methods guide, a CMA approach “*can be used when the health effects of an intervention are the same as those of the status quo”*.[15] In TA689, the submitting Company undertook an unanchored MAIC to compare acalabrutinib with ibrutinib in patients with previously treated R/R CLL. A statistically significant difference was not demonstrated for PFS or OS between the two treatments, resulting in the submitting Company concluding that the results of the MAIC demonstrate that the efficacy of acalabrutinib in PFS and OS in patients with R/R CLL is at least equivalent to that of ibrutinib. The EAG concluded that it was reasonable to assume clinical equivalence of acalabrutinib and ibrutinib in patients with previously treated R/R CLL. Results from the MAIC were used to justify the use of a CMA approach for decision making and this approach was accepted by the Committee. Zanubrutinib is a next-generation BTKi and results of the ALPINE trial, MAICs and clinical expert opinion support the plausible equivalence of zanubrutinib compared to alternative BTKis. The Company acknowledges that there is uncertainty associated with the cost-minimisation approach. However, the models were built as a cost-utility model and include all the appropriate functionality to conduct a cost-utility analysis. For the

		Company base case, a cost-minimisation approach was adopted by assuming equivalent efficacy and safety profile for all treatments. In all scenarios conducted by both the Company and the EAG in which a cost-utility approach was adopted, zanubrutinib remained below NICE's willingness-to-pay threshold with results consistent when tested both deterministically and probabilistically. By varying the MAIC hazard ratios (HRs) in accordance with the uncertainty of the respective distributions, the probabilistic analysis accounts for the uncertainty in the HRs between zanubrutinib and acalabrutinib and between zanubrutinib and ibrutinib. As outcomes still favoured zanubrutinib when run probabilistically, it is plausible to assume that zanubrutinib is at least clinically equivalent to acalabrutinib and ibrutinib and a cost-minimisation approach is justified.
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL **Issue 7:** Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	Yes	The Company are confident that the SLR captured all relevant studies reporting utility values given that the methods used were in line with the NICE literature searching and evidence submission guidelines.[7–11] Details on the time frame in which the SLR was conducted and the search strategy are included in Issue 2. The EAG recognised that filter adaptation is not unusual and therefore alleviating the concern around the health state utility value filter being adapted for use in Embase.com. As a CMA has been used in the Company base case, the choice of utility values will not affect the cost-minimisation estimates. However, to alleviate the concerns of the EAG and assess the impact of alternative utility values on cost-effectiveness, the Company has reviewed previous utility values accepted by NICE in past CLL appraisals. The alternate utility values the Company explored are presented in Table 2 and Table 3 for the untreated and R/R CLL populations, respectively. In all recent appraisals for both previously untreated and R/R CLL, the PD utility of 0.6 has been deemed appropriate as derived from Holzner *et al.* (2004).[2,13,26–28] Various scenarios using the PD utility values from ALPINE or SEQUOIA, or any decrements due to progression derived from the trial data are not deemed relevant, given that the PD trial utility values lacked face validity. Hence the Company deem it appropriate to maintain the value of 0.6 for the PD utility value. On the other hand, the progression-free (PF) utility has varied across appraisals. The PF utility value used in the base-case analysis

for the untreated model was similar to that reported in TA689, however, a lower value was reported in TA663 and GID-TA10746. The PF utility value used in the base-case analysis for the R/R model was the same as that reported in TA561, whereas TA689 used a higher utility for this health state.

As presented in Table 2 and Table 3, the use of alternative utilities that have been considered suitable by NICE Committees for decision-making does not affect the conclusions of the cost-utility analyses (CUAs) where zanubrutinib remained cost-effective in all scenarios. This is consistent with the EAG's conclusion, that across all scenarios conducted by the EAG and Company, zanubrutinib remained the preferred treatment compared with acalabrutinib and ibrutinib. Hence, the Company do not believe that use of additional alternative utility values would have an impact on the conclusions drawn from the cost-effectiveness model.

Table 2: Utility scenarios in previously untreated model (CUAs)

Source	Health state	Utility	ICER vs Ibrutinib	ICER vs acalabrutinib
Company utility values	PF	0.783	Dominant	Dominant
	PD	0.600		
TA689[25]	PF	0.780*	Dominant	Dominant
	PD	0.600		
TA663[29]	PF	0.670	Dominant	Dominant
	PD	0.600		
GID-TA10746[4]	PF	0.670	Dominant	Dominant
	PD	0.600		

ICER – Incremental cost-effectiveness ratio; PD – Progressed disease; PF – Progression free; vs – versus; SW – Southwest. **Note.** An ICER in the SW quadrant needs to be greater than the willingness-to-pay threshold to be considered cost-effective. *In instances where data has been marked up for the base case used in the appraisal, the utilities provided as a scenario by the EAG have been used.

Table 3: Utility scenarios in R/R model (CUAs)

Source		Utility	ICER vs Ibrutinib	ICER vs acalabrutinib (ICER)

<table>
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<table>
<tr><td rowspan="2">Company utility values</td><td>PF</td><td>0.7480</td><td rowspan="2">Dominant</td><td rowspan="2">Less costly and less effective [redacted]</td></tr>
<tr><td>PD</td><td>0.6000</td></tr>
<tr><td rowspan="2">TA689</td><td>PF</td><td>0.7800*</td><td rowspan="2">Dominant</td><td rowspan="2">Less costly and less effective [redacted]</td></tr>
<tr><td>PD</td><td>0.6000</td></tr>
<tr><td rowspan="2">TA561</td><td>PF</td><td>0.7480</td><td rowspan="2">Dominant</td><td rowspan="2">Less costly and less effective [redacted]</td></tr>
<tr><td>PD</td><td>0.6000</td></tr>
</table>
ICER – Incremental cost-effectiveness ratio; PD – Progressed disease; PF – Progression free; vs – versus; SW – Southwest; R/R – relapsed/refractory. Note. An ICER in the SW quadrant needs to be greater than the willingness-to-pay threshold to be considered cost-effective. *In instances where data has been marked up for the base case used in the appraisal, the utilities provided as a scenario by the EAG have been used.
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<td>Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL</td>
<td>No</td>
<td>Whilst the Company acknowledges that data from the SEQUOIA and ALPINE trials are immature, the cost-effectiveness models make the best use of the data available. The issue of immature trial data is not new in the CLL landscape, as patients can live for a long time with current treatments. This issue has been evident across several previous CLL appraisals. In TA689, a similar median follow-up was reported for acalabrutinib monotherapy in ELEVATE-TN (28.4 months) as that reported in the zanubrutinib arm of SEQUOIA (16.35 months) in previously untreated CLL. Furthermore, a shorter follow-up was reported in the acalabrutinib arm of ASCEND (16.0 months) compared to the zanubrutinib arm of ALPINE (23.82 months) in R/R CLL. OS data from both ELEVATE-TN and ASCEND were immature, with median OS not reached in any treatment group. Similarly, immature OS data was evident in both the GLOW and CAPTIVATE trials reported in TA10746. The level of data immaturity reported in the zanubrutinib clinical trials is therefore aligned with that in previous appraisals.[4,25]

The process of selecting a best-fitting distribution for extrapolation of survival data was aligned with the NICE DSU 14 guidelines.[30] Selection involved an assessment of clinical plausibility leveraging clinical expert opinion and comparing to published trial data, coupled with an assessment of statistical fit via measures such as Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). The Company explored the impact of alternative survival functions within their scenario analyses, and further</td>
</tr>
</table>

		scenario analyses were also conducted by the EAG. In all scenarios presented, zanubrutinib remained cost-effective.

Additional issues

No additional issues were identified.

Summary of changes to the company's cost-effectiveness estimate(s)

The Company has not submitted a revised base case.

Sensitivity analyses around revised base case

Not applicable.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 17 May.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating chronic lymphocytic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr RE Johnston
2. Name of organisation	University Hospitals Sussex
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic lymphocytic leukaemia? ☒ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for chronic lymphocytic leukaemia?	CLL is a cancer characterised by uncontrolled proliferation of lymphocytes within the bone marrow and/or lymph nodes. This leads to progressive bone marrow failure and/or worsening lymphadenopathy. The aim of treatment is to induce

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	remission by clearing disease within the bone marrow and nodes and improve both progression free and overall survival. There is no cure currently for CLL and treatments have limited efficacy and associated toxicities. A regime with greater efficacy leads to resolution and maintenance of normal marrow function, control of lymphadenopathy and improved overall survival. In addition, as survival improves, the impact of therapies on longer term effects such as secondary cancer, cardiovascular health and Richter's transformation are increasingly important.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Response in CLL is measured by the internationally standardised IWCLL criteria (International Workshop on Chronic Lymphocytic Leukaemia). It is generally accepted that partial or complete responses are acceptable, provided they are accompanied with resolution of CLL-related symptoms We look for resolution of lymphadenopathy and bone marrow function and with some therapies we also look for very deep remissions in the blood and bone marrow, using flow cytometry or next generation sequencing.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	Until the recent NICE appraisal ID3860, the unmet need most relevant to this appraisal was the absence of NICE approved BTKi for patients in front line, who would otherwise have been considered fit for chemoimmunotherapy (CIT) and had non-disrupted TP53 status. Now these patients can access *fixed duration* Ibrutinib plus Venetoclax (15 months) in addition to the already available Venetoclax plus Obinotuzumab (1 year) There is still no up-front access, however, to *continuous* BTKi for these younger patients with non-disrupted TP53 and there is as yet, limited data available on the impact of fixed duarion vs continous regimes on PFS and OS. This sub-group of younger patients however still cannot choose a continuous BTKi regime. Further data is need on optimal combination and sequencing of targeted agents especially in the context of treating patients relapsing following fixed duration I plus V.

	The treatment of CLL patients who fail all existing and available drug-classes, however, is perhaps the biggest unmet need. Despite the recent approval of novel agents for treatment of CLL, which are now readily available in the treatment pathway, there is still a significant subgroup of patients for whom treatment options are exhausted and who die of progressive CLL.
11. How is chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	**<u>Untreated CLL</u>** Just proved for all patients: Fixed duration I plus V *Recommendations (NICE approved), from latest UK BCSH Guidelines:* • Venetoclax-obinutuzumab (VenO) or acalabrutinib are recommended and NICE-approved options as initial therapy in patients unsuitable for CIT irrespective of TP53 status • Bendamustine or chlorambucil-based CIT are no longer recommended. • NICE-approved treatment options for fit patients with TP53 disruption include acalabrutinib, ibrutinib or venetoclax monotherapy for those with a contra-indication to B-cell receptor inhibitor. • Acalabrutinib is recommend for patients who have intact TP53 and for whom FCR or BR are considered unsuitable. • For fit patients with intact TP53, VenO may be obtained via CDF. • For fit patients with intact TP53 and with mutated IGHV, chemo-immunotherapy with FCR remains an acceptable initial therapy • Idelalisib with rituximab (17p deletion or TP53 mutation) *Recommendations (not NICE approved):*

	• Acalabrutinib-obinutuzumab is a frontline treatment option or all patients with or without TP53 disruption • Ibrutinib monotherapy is a frontline treatment option for all patients with or without TP53 disruption • *Subject to ongoing NICE appraisal:* • Zanubrutinib • **Relapsed and refractory CLL** *Recommendations (NICE approved), from latest UK BCSH Guidelines:* • Targeted inhibitors (BTKi or BCL2i alone or in combination with rituximab) are the treatment of choice for relapsed CLL. In England and Wales, ibrutinib, acalabrutinib, and venetoclax with or without rituximab are currently approved and commissioned for this indication. • For patients relapsing after BTKi offer venetoclax-based regimens, irrespective of *TP53* status. • For patients relapsing following fixed-duration venetoclax-based therapy consider either a BTKi or venetoclax retreatment depending on duration of PFS1. • For relapsed patients who are intolerant to ibrutinib, offer either venetoclax-based therapy or acalabrutinib depending on the reason for intolerance. • Idelalisib–rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment. (GRADE IIB).

	• Patients with double refractory CLL after BTKi and BCL2i should be considered for clinical trials *Subject to ongoing NICE appraisal:* • Zanubrutinib *May also be able to access Pirobrutunub currently on compassionate access scheme if pre-exposed to all other agents* **<u>Guidelines</u>** • Renata Walewska, Nilima Parry-Jones, Toby A. Eyre, George Follows, Nicolas Martinez-Calle, Helen McCarthy, Helen Parry, Piers E. M. Patten, John C. Riches, Peter Hillmen, Anna H. Schuh Guideline for the treatment of chronic lymphocytic leukaemia, BJHaem 2022 • Chloe Pek Sang Tang, Gregory Y.H. Lip, Terry McCormack, Alexander R. Lyon, Peter Hillmen, Sunil Iyengar, Nicolas Martinez-Calle, Nilima Parry-Jones, Piers E.M. Patten, Anna Schuh, Renata Walewska, on behalf of the BSH guidelines committee, UK CLL Forum Management of cardiovascular complications of bruton tyrosine kinase inhibitors. *British Journal of Haematology,* 2022; **196**: 70-78. • Eyre TA, Riches JC, Patten PEM, Walewska R, Marr H, Follows G, et al. Richter transformation of chronic lymphocytic leukaemia: a British Society for Haematology Good Practice Paper. *Br J Haematol*. 2022; **196**(4): 864– 70.

	• Clinical Practice Guidelines – Chronic Lymphocytic Leukaemia (esmo.org) • iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL | Blood | American Society of Hematology (ashpublications.org)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology can be adopted onto existing clinical pathways which exist for Ibrutinib and Acalabrutinib. Because of this no investment would be required to implement the TA.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	In the upfront setting, we do not yet have any direct comparison between Acalabrutinib, Zanubrutinib and VenO, but there is limited evidence to suggest that patients with high risk disease – p53 deletion/ mutation – have longer PFS on BTKi. Zanubrutinib will definitely lead to less AF and discontinuations and it appears that sudden cardiac death is reduced on this drug. Also, young patients with an unmutated IgVH gene have shorter PFS on Ven-O and cannot currently access a BTKi. Zanubrutinib also demonstates superiority over ibrutinib in this patient group in the R/R setting in the Alpine trial and so is likely also to provide benefit in the upfront setting.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with pre-existing cardiac disease are likely to tolerate Zanubrutinib better and so get full clinical benefit. Limited evidence that patients who have dose-limiting toxicity with Ibrutinib or Acalabrutinib can tolerate Zanubrutinib. Zanubrutinib appears superior in patients with TP53 disrupted disease and has excellent efficacy in IgVH unmutated patients.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Will be used in the same way as existing BTKis, so no additional costs or practical issues to implement TA.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	IwCLL and BSH guidelines will be used to assess when patients need to start treatment. Currently we continue medication until disease progression.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	It is difficult to model the QOL benefits associated with not developing AF, an ongoing arrhythmia requiring either discontinuation of therapy or accepting increased bleeding risks whilst continuing both BTK therapy.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Technology is very similar to existing Acalabrutinib; in fact the company have presented it as non-inferior. No direct comparison either from trials or the real world is available.

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As previously discussed, the reduced incidence of cardiac arrhythmias
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trials represent the available treatment choices in the UK at the time of the trial. These choices have evolved with new evidence and NICE TAs, but the results remain entirely relevant to UK practice. In the R/R setting, the randomised phase 3 ALPINE R/R trial is comparable with UK clinical practice, comparing Zanubrutinib to Ibrutinib (currently available in this setting in the UK) in patients who had received at least one course of therapy. At 24 months, PFS was superior in the investigational arm (78.4% vs 75.9% p=0.002). In addition, Zanubrutinib had improved PFS across all subgroups, including those with p53 deletion or mutation. Overall response was higher and discontinuation rates lower; with a reduction in cardiac events and deaths in Zanubrutinib patients. Data in untreated patients compared Zanubrutinib to R-Bendamustine. This was an appropriate comparator with UK practice at the time of the SEQUIA trial design in patients >65, or not fit enough for FCR. Median PFS was not reached (95% CI: NE, NE) in the zanubrutinib cohort compared with 33.7 months (95% CI: 28.1, NE) in the BR cohort (HR= 0.42, 95% CI: 0.28, 0.63; p=<0.0001). Since the positive NICE appraisals for Ven-O and Acalabrutinib, however, it now very rare for CIT to be offered as first line therapy. In addition, in fit and young patients, we know that Ibrutinib is superior to both R-Bendamustine and FCR (the previous gold standard therapy) in a Phase 3 upfront setting. Given that we see reduced arrhythmic adverse effects, reduced discontinuations and improved PFS in the R/R setting with Zanubrutinib vs

	Ibrutinib in CLL (and in all settings in other B-cell malignancies) it seems likely that Zanubrutib will also be a superior BTKi in the front-line setting and afford significant benefit to our young patients in the UK, who cannot currently access a BTKi. Finally, in both settings, there is some limited evidence that Zanubrutinib is better tolerated even in patients who have had issues on Acalabrutinib.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Nothing else
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of following NICE technology appraisal guidance: • **TA796** • **TA689** • **TA663** • **TA561** • **TA429** • **TA359** • **TA343** • **TA216** • **TA174** • **TA119** • **TA193** • **TA29**	TA796 • Not aware of any updates since recent appraisal TA689 • Not aware of any published updates TA663 • Al-Sawaf, O., Zhang, C., Jin, H.Y. *et al.* Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. *Nat Commun* **14**, 2147 (2023) TA561: • Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. Blood. 2022;140(8):839-850. TA429 • Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Kipps TJ, Moreno C, Montillo M, Burger JA, Byrd JC, Hillmen P, Dai S, Szoke A, Dean JP, Woyach JA. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019 Dec;94(12):1353-1363. TA359: • Paolo Ghia, Steven E. Coutre, Bruce D. Cheson, Jacqueline C. Barrientos, Peter Hillmen, Andrew R. Pettitt, Andrew D. Zelenetz,

	Sanatan Shreay, Michael Hallek, Richard R. Furman. Impact of idelalisib on health-related quality of life in patients with relapsed chronic lymphocytic leukemia in a phase III randomized trial. Haematologica 2020;105(10):e51 TA343 • Not aware of any updates None of the remaining appraisals listed below contain relevant drugs TA216 TA174 TA119 TA193 TA29
23. How do data on real-world experience compare with the trial data?	There is limited real-world data on Zanubrutinib in CLL. An abstract compared BTKis retrospectively in a comparable B-cell malignancy, Mantle Cell Lymphoma (MCL), The study reviewed 300 patients; (3x100 exposed to each of zanubrutinib, ibrutinib or acalabrutinib) outside of clinical trials. Whilst patients treated with zanubrutinib were older and had more complex MCL baseline features at initiation, multivariable regression suggested a trend favouring zanubrutinib over ibrutinib or acalabrutinib for both response and adverse events. *Real-world (RW) treatment patterns and comparative effectiveness of Bruton tyrosine kinase inhibitors (BTKi) in patients (pts) with mantle cell lymphoma (MCL).* *Bijal D. Shah, Keri Yang, Andrew J. Klink, Tom Liu, Todd M. Zimmerman, Ajeet Gajra, and Boxiong TangJournal of Clinical Oncology 2022 40:16_suppl, e18727-e18727*
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	Younger patients with an intact p53 gene do not have equal access to BTKi in the upfront setting. We now know that the other BTK inhibitors are superior to CIT in the upfront setting in younger patients. It seems very unlikely that the benefit seen in those

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	trials, which mirrored results in older patients will not be seen in Zanubrutinib in the same group. Abolishing the historical definition of fit vs unfit would allow access to all.

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Exclusion of venetoclax-rituximab (VenR) as an eligible comparator in relapsed/refractory chronic lymphocytic leukaemia (R/R CLL) **Question:** Is VenR a relevant comparator to zanubrutinib in the R/R CLL population?	The BCSH Guidelines are developed in the context of both published evidence and NICE approved available options, and are referenced widely. The CS used market survey data on Ventoclax usage, either as a single agent, or in combination with Rituximab, to exclude it as comparator for Zaunubrutinib, The information gleaned from these surveys was that Venetoclax was typically used to treat more “fit“ patients. The company rather have positioned Zanubrutinib as an alternate BTKi choice to Ibrutinib and Acalabrutinib. For the UK haematologist, however, it remains a recommended treatment option in R/R CLL. During the COVID pandemic, clinicians tried to avoid initiating any therapy that would increase in-hospital attendance and thus risk of COVID exposure for patients. Venetoclax therapy requires multiple hospital visits over the first 4-5 weeks of treatment for blood tests and monitoring. BTKi therapy is more straightforward to initiate and does not require in-hospital monitoring. This meant that any Venetoclax-based treatment was avoided, if at all possible, during the pandemic. This may have skewed any market survey data conducted in its wake. Veneoclax-based treatment for R/R patients remains a valid treatment option for • Patients relapsing after CIT who prefer a time-limited treatment option • Patients relapsing after CIT with significant cardiac issues where clinician preference might be to avoid a BTKi

	• Patients relapsing after newly approved V plus I treatment Some limited data is available on re-treatment with Venetoclax following an initial venetoclax-based regime (see Abstract 5201 for pending EHA 2023 conference ORR 72% and mPFS 23.3 months in retreated patients in the MURANO study)
Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL **Question:** Are there any relevant clinical studies not included in the company submission for untreated CLL and R/R CLL? If so, what is the likely impact of these on the clinical and cost-effectiveness of zanubrutinib versus comparators?	The concerns of the EAG centre around potential data missed due to • the use of a single database to interrogate all other databases, rather than individual searches for each database • potential alterations of study design filters and the impact this would have on filter perfomance • limited search criteria, i.e. using only one search term "CLL" ; rather than also using alternative spelling and search terms • non-standard methods for searching for conference "grey literature" Not expert in this area, but presume that a similar issue with new drugs would be new and maturing data emerging between the literature search cut-off and time of actual appraisal? By excluding Veneoclax, the CLL14 trial (VenO – upfront) and the Murano trial (VenR – R/R) have not been considered.
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison **Question:** Is the cohort 1 of SEQUOA trial reflective of population 'unfit' to	In the SEQUOIA trial for untreated CLL, patients were randomised to either Zanubrutinib or BR. By the company's own definition those patients would have been considered "fit" for BR to be able to be randomised, whilst the CS actually excludes this "fit" population with intact p53 and seeks approval for the "unfit" population only. Historically, the term "unfit" was used to define patients in whom the treatment toxicity associated with CIT would limit the clinician's ability to deliver it. In this "unfit" population, CIT would lead to unacceptable and potentially life-threatening side effects and thus poorer outcomes.

receive FCR or BR therapy? If not, is it appropriate to consider cohort 1 as a proxy for the 'unfit' population?	FCR is the most toxic regime; BR slightly less so, but it is very rare indeed now for either regime to be used due to the superior efficacy and improved tolerability of new agents. The separation of "fit" and "unfit" patients is now largely redundant. Treatment choices are now made jointly by clinician and patient, based on disease related characteristics (eg TP53 and IGHV status) and patient preference (short vs long-term treatment/ ability to attend for monitoring/ cardiac co-morbidities). As yet, there are only limited indirect comparisons to be made, between different trials, as to the superiority of any regime or the optimal sequence in which they should be used. Nonetheless, in SEQUOIA, all patients would have had to be "fit enough" to tolerate BR. The first concern must therefore be whether Zanubrutinib would be more toxic when used in the "unfit" population who will get access through this TA. In answer to this; we already know that Ibrutinib and Acalabrutinib can be safely delivered in the "unfit" population both upfront and in the R/R setting as initial trials were done in this group. We also know that the toxicity and discontinuation rates of Zanubrutinib compare favourably with Ibrutinib in the R/R setting in the Alpine trial. It thus seems likely that this reduced toxicity will also be observed in the upfront setting compared with Ibrutinib and likely Acalabrutinib. I cannot comment on whether this will affect the calculations, but having BR as the comparator in the SEQUOIA trial should not lead to unexpected adverse events when used in the real world in the unfit population. Secondly, we are not clear why the company has chosen not to use this SEQUOIA data as evidence for the use of Zanubrutinib upfront in a "fitter" population, who currently have the unmet need in the UK of being able to access continuous, single-agent BTK therapy. If the appraisal committee were to accept that the differentiation between "fit" and "unfit" was now redundant; could they consider approving access for all?
Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL	The EAG rejects the company's assertion that Zanubrutinib is non-inferior to Acalabrutinib using the MAIC due to the confidence intervals observed for the hazard ratios. The CS does make some reference to this in Section B.2.1.1.2. It also sounds like this was commented on by experts in the advisory board used by the company. Even so, the pre MAIC values for OS and PFS in untreated patients are similar, suggesting that Zanubrutinib as an intervention is very similar to Acalabrutinib, even though it cannot be considered statistically non-inferior based on the MAIC.

Question: Based on the MAIC analysis, is the company's assumption of non-inferiority between zanubrutinib and relevant comparators for untreated CLL and R/R CLL appropriate?	In fact, the pre-matched SEQUOIA population had more patients with disrupted p53 than the ELEVATE-TN patients so may in fact be more effective. Unable to comment as clinicians on the impact which this will have on the economic evaluation in the TA.
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL **Question:** Are there any relevant studies reporting on health related quality of life of patients with untreated CLL and R/R CLL that have not been included in the company submission?	Similar to Issue 2, the EAG has concerns that the SLR was insufficiently sensitive to capture all clinical studies of interest and the rationale for the actual filters chosen was unclear. In addition, the lack of more recent searches of conference abstracts beyond July 2022 was of concern and this may be more relevant for health utility values which are often published after the initial trial results and often in abstract form at conferences.
Issue 6: Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	As in Issue 4, the EAG rejects the company's assertion that Zanubrutinib is non-inferior to Acalabrutinib using the MAIC. Because of this, the CMA used to compare cost of the two interventions was the wrong economic evaluation, as the CMA requires robust confirmation of equivalence (non-inferiority) for both interventions.

	In the R/R setting in the ALPINE trial, the CS shows that Zanubrutinib confers a statistically significant 31% reduction in PFS or death at the Aug 22 data cut off when directly compared to Ibrutinib, thus confirming superiority rather than equivalence. This adds further weight to the EAG concerns in that respect Despite the statistical difficulties, the available data suggests that Zanubrutinib has significantly lower rates of dose-limiting toxicicty. In fit and young patients, we know that Ibrutinib is superior to both R-Bendamustine and FCR (the previous gold standard therapy) in a Phase 3 upfront setting. Given that we see reduced arrhythmic adverse effects, reduced discontinuations and improved PFS in the R/R setting with Zanubrutinib vs Ibrutinib in CLL (and in all settings in other B-cell malignancies) it seems likely that Zanubrutib will also be a superior BTKi (vs Ibrutinib) in the front-line setting and afford significant benefit to our young patients in the UK, who cannot currently access single-agent BTKi. In both settings, there is some limited real world evidence that Zanubrutinib is better tolerated even in patients who have had issues on Acalabrutinib – see ref below. Cardiovascular adverse events associated with BTKi therapy may interfere with continuation of best possible care, induce life-threatening CV complications or lead to long-term morbidity including worse CLL-related outcomes if optimal BTKi treatment is withheld. Zanubrutinib with a lower risk of development of AF and a reduced risk of sudden cardiac death (even in relation to Acalabrutinib) is likely to bring significant quality of life benefits to all BTKi eligible patients. All published studies show that Zanubrutinib is better tolerated than Ibrutinib. The impact of tolerability, and thus, the ability to maximise response, (especially to first line treatment), is difficult to assimilate into the economic evaluation over 30 years. As a clinician, it seems likely that the impact for individual patients will be significant, however, we are unable to comment of the impact of this on economic evaluation. Real-world (RW) treatment patterns and comparative effectiveness of Bruton tyrosine kinase inhibitors (BTKi) in patients (pts) with mantle cell lymphoma (MCL). Bijal D. Shah, Keri Yang, Andrew J. Klink, Tom Liu, Todd M. Zimmerman, Ajeet Gajra, and Boxiong Tang Journal of Clinical Oncology 2022 40:16_suppl, e18727-e18727
Issue 7: Uncertainty in the utility estimates used in the company economic model in	The EAG criticises the CS as it does not use utility values collected from the compared trials; rather, the company used values from an UK general age-sex matched population, and does not address the uncertainty in these values.

untreated CLL and R/R CLL **Question:** Are the estimates of the health-related quality of life in the company submission reflective of patients with untreated CLL and R/R CLL?	The EAG went on to explore scenarios using actual utility values from the SEQUOIA and ALPINE trials and found that because of the cost savings with Zanubrutinib, changes to utility values had a minimal effect on overall conclusions. So it appears that Issue 7 is unlikely to impact on the outcome of the TA.
Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	The effectiveness of Zanubrutinib means that within the time frame of the trial so far reported (<30.5 months), there are few progression events or deaths. This means that the survival curves for the 30 year horizon for the evaluation must be based on parametric models. There are a wide variety of these. The EAG would have preferred more exploration of various models in the CS. The company did apply alternative survival curves to PFS and OS as part of their scenario analyses only and the EAG conducted further scenario analyses not modelled by the company. Alternative models did change the incremental results for costs and QALYs but did not alter overall conclusions. It would seem sensible to collect real world data to inform the accuracy of these models and perhaps help in future appraisals.
Issue 9: Uncertainty in untreated “high-risk” CLL subgroup	The NICE scope for this TA required data from subgroup analyses for those with p53 disruption in the untreated population. In this population in the UK, both Ibrutinib and Acalabrutinib are available. The SEQUOIA trial recruited patients with TP53 disruption (n=110) into a separate cohort who all received Zanubrutinib. At a median follow-up of 27.7 months, PFS was not reached. For Ibrutinib, the company used data from the ALPINE trial which is a direct comparison between the 2 drugs, but was conducted in the R/R population. Patients with p53 disruption in the R/R setting do not have the same genetic profile as patients with p53 disruption in the untreated setting. For Acalabrutinib, the CS focused on the 2020 Sharman Lancet publication on ELEVATE-TN, which does not contain any data on the relevant subgroups. In a more recent letter with a median follow-up of 46.9 months for the

	same trial, median PFS was not reached in the acalabrutinib-containing arms in patients with del17p and/or mutated *TP53* (n=82). Demographic data on the characteristics of this subgroup was not published. Thus, data is limited and direct comparisons impossible. Real world data and longer term follow-up will inform some comparisons but this will take years. Ref: Sharman, J.P., Egyed, M., Jurczak, W. *et al.* Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia* 36, 1171–1175 (2022)
Are there any important issues that have been missed in EAR?	Important not to discount the unmet need for single agent BTK in younger patients who currently do not have access

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Zanubrutinib is an effective BTKi with a favourable side-effect and efficacy profile compared with Ibrutinib, and likely similar to Acalabrutinib
No sudden cardiac deaths have yet been reported with Zanubrutinib, in contrast to the other BTKis
The differentiation between fit and unfit patients is redundant; decisions are now based on disease characteristics and patient choice

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 17 May.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Comments received during engagement 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating chronic lymphocytic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Francesco Forconi
2. Name of organisation	University of Southampton (Hospital Trust)
3. Job title or position	Professor of Haematology and Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic lymphocytic leukaemia? ☒ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No direct or indirect links to, or funding from, the tobacco industry
8. What is the main aim of treatment for chronic lymphocytic leukaemia?	To achieve a durable response with a limited toxicity

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	I consider clinically signficant any response with reduction of the tumor burden superior than 50% according to iwCLL criteria (PR, CR, CRi)
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	In my view the most relevant unmet needs are i) to improve quality and duration of response and safety profile; ii) to reduce signficanctly costs of care of patients on active treatment (cost of drug, number of appointments, blood tests, hospitalisation, etc due to monitoring or adverse events, etc..) and iii) prevent transformation in high-grade lymphoma (Richter's syndrome)
11. How is chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	CLL current treatment strategy is according to the BSH guidelines. However, the pathway of care still needs improvement: For example, there are new treatments, like the combination of a BTKi and BH3 mimetic (I+V) that has just been approved by NICE, but they still need to be interpreted on how they work in practice and in real-life: there are toxicities that we cannot yet measure in real life (e.g. neutropenias, infections, cardiac toxicity, other non specific toxicities) so they currently cannot be used as comparators. Another criticial point is that we do not know the sequencing of the novel drugs. In certain circumstances we do not know what we can offer if patients fail concomitant BTKi and BH3 mimetics. As another example there is a suggestion from indirect comparisons that acalabrutinib may be preferred over venetoclax-based regimens in TP53 disrupted. There is a need to improve efficacy and reduce the toxicity of BTKi, while also reducing their costs. Zanubrutinib would be able to impact in a setting similar to acalabrutinib, Zanubrutinib has superior PFS than immunochemotherapy (BR) and similar atrial fibrillation risk as BR in treatment-naïve, unfit, wild type TP53 patients, and may be less expensive than other BTKi for all TP53mut/del, including patients who were treated previously with venetoclax-based regimens.

	However, a Venetoclax-based regimen may be preferred if a patients was previously treated with a BTKi.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Please refer to the comments above
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Alpine study has documented clinical signficant benefit of zanubrutinib over 1st generation BTKis for improved ORR, PFS and safety (AF).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Please refer to the comments above
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	Zaqnubrutinib is an oral drug which is not expected to cause significant difficulties for its use and administration, while it would be expected to be cheaper than other BTKIs if approved.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would be beneficial to stratify patients for mutational status of the IGHV and for mutation or deletion of TP53
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Zanubrutinib would be expected to be cheaper than other BTKIs if approved.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Zanubrutinib would be improving efficacy and safety profile compared to other BTKis (Alpine study). One would expect Zanubrutinib to be cheaper than other BTKIs if approved and have a social impact by reducing heralth care costs
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Cardiovascular complications are a major xicity of BTKis - Zanubrutinib has less atrial fibrillation complications and is safer than ibrutinib in the Alpine study
20. Do the clinical trials on the technology reflect current UK clinical practice?	The current clinical trials Sequoia (treatment-naïve, unfit TP53 non deleted – zanubrutinib vs BR in cohort 1; or TP53 deleted – single arm in cohort 2) and Alpine (R/R CLL, ibrutinib vs zanubrutinib) have confirmed that chemotherapy is

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	not needed anymore in CLL and BTKi like ibrutinib are more toxic and less efficient.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of following NICE technology appraisal guidance: • **TA796** • **TA689** • **TA663** • **TA561** • **TA429** • **TA359** • **TA343** • **TA216** • **TA174** • **TA119** • **TA193** • **TA29**	No
23. How do data on real-world experience compare with the trial data?	Not much RWE available with zanubrutinib

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	No awarness of equality issues

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Exclusion of venetoclax-rituximab (VenR) as an eligible comparator in relapsed/refractory chronic lymphocytic leukaemia (R/R CLL) **Question:** Is VenR a relevant comparator to zanubrutinib in the R/R CLL population?	VenR would be a relevant comparator to zanubrutinib in the R/R CLL population, but I am not aware of trials directly comparing these regimens.
Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of	Although there are other treatments used in untreated and R/R, I am not aware of systematic reviews or head-to-head direct comparisons with these treatments. However by indirect comparison, zanubrutinib appears equivalent to acalabrutinib

interest in untreated CLL and R/R CLL **Question:** Are there any relevant clinical studies not included in the company submission for untreated CLL and R/R CLL? If so, what is the likely impact of these on the clinical and cost-effectiveness of zanubrutinib versus comparators?	
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison **Question:** Is the cohort 1 of SEQUOA trial reflective of population 'unfit' to receive FCR or BR therapy? If not, is it appropriate to consider cohort 1 as a proxy for the 'unfit' population?	Sequoia is demonstrating that Zanubrutinib is beneficial for efficacy and toxicity over BR immunochemotherapy

Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL **Question:** Based on the MAIC analysis, is the company's assumption of non-inferiority between zanubrutinib and relevant comparators for untreated CLL and R/R CLL appropriate?	The MAIC results demonstrated ORR and PFS benefits for ZANU vs IBRU in R/R MZL. Although very comforting and supportive of Zanubrutinib over ibrutinib as in the Alpine study, MAIC does not provide data applicable to CLL.
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL **Question:** Are there any relevant studies reporting on health related quality of life of patients with untreated CLL and R/R CLL that have not been included in the company submission?	Not aware of relevant studies reporting on effect of zanubrutinib on health related quality of life of patients with untreated CLL and R/R CLL

Issue 6: Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	Ideal that zanubrutinib, if approved, be cheaper than any other BTKi
Issue 7: Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL **Question:** Are the estimates of the health-related quality of life in the company submission reflective of patients with untreated CLL and R/R CLL?	Ideal that zanubrutinib, if approved, be cheaper than any other BTKi
Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	Not concerned that Sequoia and Alpine study are immature for the decision to approve zanubrutinib
Issue 9: Uncertainty in untreated "high-risk" CLL subgroup	Current data clearly indicate a benefit of any BTKi in high-rispk patients, with evidence that zanubrutinib is superior than ibrutinib in the Alpine study
Are there any important issues that	N/A

have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Zanubrutinib formally superior than immunochemotherapy

Zanubrutinib has a better PFS than ibrutinib

Zanubrutinib has less AF than ibrutinib

There are no direct comparisons with acalabrutinib

Cost of zanubrutinib would be critical

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Technical engagement response form

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Information on completing this form

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Chronic Lymphocytic Leukaemia Support Charity
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	Most recent funding information AstraZeneca – £15,000 Core funding of member services Abbvie - £12,000 Core funding of member services Roche – £16,000 Core funding of member services Janssen - £7,500 Core funding of member services Beigene - NONE
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**No**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL	Yes/No	No additional comments
Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL	Yes/No	Unable to comment
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison	Yes/No	No additional comments
Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL	Yes/No	Unable to comment
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies	Yes/No	Unable to comment

reporting utility values in untreated CLL and R/R CLL		
Issue 6: Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	Yes/No	Unable to comment
Issue 7: Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	Yes/No	Unable to comment
Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	Yes/No	Unable to comment
Issue 9: Uncertainty in untreated "high-risk" CLL subgroup	Yes/No	Unable to comment

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

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Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

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Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL	Yes/No	No comment
	Yes/No	No comment
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison	No	It is important that all parties recognise the strong unmet need across all subgroups of CLL patients, including in the fit population. This is an unmet need in first line and relapsed/refractory settings which Zanubrutinib could address. The patients who might need this treatment are not only those who cannot have cancer immunotherapies (CIT) due to unfitness, as CIT is no longer used routinely in clinical practice for either fit or unfit patients. As such this definition of fitness is not appropriate, and in practise there are fewer options for fit patients. In addition, there will be some patients with an unmet need due to an inability to have some of the other treatments recently approved in this setting, such as the venetoclax based therapies. It is possible that some people could benefit from Zanubrutinib but not from the newer therapies.

Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL	Yes/No	No comment
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL	Yes/No	No comment
Issue 6: Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	Yes/No	No comment
Issue 7: Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	Yes/No	No comment
Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	Yes/No	No comment
Issue 9: Uncertainty in untreated "high-risk" CLL subgroup	Yes/No	No comment

Additional issues

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NICE National Institute for Health and Care Excellence

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Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

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<table>
<tr><td>Your name</td><td>[redacted]</td></tr>
<tr><td>Organisation name: stakeholder or respondent
(if you are responding as an individual rather than a registered stakeholder, please leave blank)</td><td>UK CLL Forum, British Society for Haematology and the Royal College of Pathologists</td></tr>
<tr><td>Disclosure
Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.]
Please state the name of the company, amount, and purpose of funding.</td><td>For CLL Forum only
<table>
<tr><th>Company</th><th>Meeting</th><th>Amount</th></tr>
<tr><td>AstraZeneca</td><td>Both</td><td>£10,000</td></tr>
<tr><td>AbbVie</td><td>March</td><td>£5,000</td></tr>
<tr><td>Roche</td><td>March</td><td>£2,500</td></tr>
<tr><td>Janssen</td><td>March</td><td>£3,500</td></tr>
<tr><td>BeiGene</td><td>March</td><td>£5,000</td></tr>
<tr><td>AbbVie (additional – Medical)</td><td>March</td><td>£1,000</td></tr>
<tr><td>Roche</td><td>October</td><td>£2,500</td></tr>
<tr><td>BeiGene</td><td>October</td><td>£5,000</td></tr>
<tr><td>AbbVie (plus Medical)</td><td>October</td><td>£7,000</td></tr>
<tr><td>Janssen</td><td>October</td><td>£3,500</td></tr>
<tr><td>Janssen</td><td>October – Additional Virtual Pass</td><td>£300.00</td></tr>
<tr><td>AbbVie Medical</td><td>October – Additional In Person Pass</td><td>£500.00</td></tr>
<tr><td></td><td>TOTAL</td><td>£45,800</td></tr>
</table></td></tr>
<tr><td>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry</td><td>None</td></tr>
</table>

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL	Yes, but for VenO	The BCSH Guidelines are developed in the context of both published evidence and NICE approved available options, and are referenced widely. The CS used market survey data on Ventoclax usage, either as a single agent, or in combination with Rituximab, to exclude it as comparator for Zaunubrutinib, The information gleaned from these surveys was that Venetoclax was typically used to treat more “fit“ patients. For the UK haematologist, however, it remains a recommended treatment option in R/R CLL. During the COVID pandemic, clinicians tried to avoid initiating any therapy that would increase in-hospital attendance and thus risk of COVID exposure for patients. Venetoclax therapy requires multiple hospital visits over the first 4-5 weeks of treatment for blood tests and monitoring. BTKi therapy is more straightforward to initiate and does not require in-hospital monitoring. This meant that any Venetoclax-based treatment was avoided, if at all possible, during the pandemic. This may have skewed any markey survey data conducted in its wake. Veneoclax-based treatment for R/R patients remains a valid treatment option for • Patients relapsing after CIT who prefer a time-limited treatment option • Patients relapsing after CIT with significant cardiac issues where clinician preference might be to avoid a BTKi • Patients relapsing after newly approved V plus I treatment

		• Some limited data is available on re-treatment with Venetoclax following an initial venetoclax-based regime (see Abstract 5201 for pending EHA 2023 conference ORR 72% and mPFS 23.3 months in retreated patients in the MURANO study)
Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL	No	The concerns of the EAG centre around potential data missed due to • the use of a single database to interrogate all other databases, rather than individual searches for each database • potential alterations of study design filters and the impact this would have on filter perfomance • limited search criteria, i.e. using only one search term "CLL" ; rather than also using alternative spelling and search terms • non-standard methods for searching for conference "grey literature" Not expert in this area, but presume that a similar issue with new drugs would be new and maturing data emerging between the literature search cut-off and time of actual appraisal? By excluding Veneoclax, the CLL14 trial (VenO – upfront) and the Murano trial (VenR – R/R) have not been considered.
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison	No	In the SEQUOIA trial for untreated CLL, patients were randomised to either Zanubrutinib or BR. By the company's own definition those patients would have been considered "fit" for BR to be able to be randomised, whilst the CS actually excludes this "fit" population with intact p53 and seeks approval for the "unfit" population only. Historically, the term "unfit" was used to define patients in whom the treatment toxicity associated with CIT would limit the clinician's ability to deliver it. In this "unfit" population, CIT would lead to unacceptable and potentially life-threatening side effects and thus poorer outcomes. FCR is the most toxic regime; BR slightly less so, but it is very rare indeed now for either regime to be used due to the superior efficacy and improved tolerability of new agents. The separation of "fit" and "unfit" patients is now largely redundant.

		Treatment choices are now made jointly by clinician and patient, based on disease related characteristics (eg TP53 and IGHV status) and patient preference (short vs long-term treatment/ ability to attend for monitoring/ cardiac co-morbidities). As yet, there are only limited indirect comparisons to be made, between different trials, as to the superiority of any regime or the optimal sequence in which they should be used. Nonetheless, in SEQUOIA, all patients would have had to be "fit enough" to tolerate BR. The first concern must therefore be whether Zanubrutinib would be more toxic when used in the "unfit" population who will get access through this TA. In answer to this; we already know that Ibrutinib and Acalabrutinib can be safely delivered in the "unfit" population both upfront and in the R/R setting as initial trials were done in this group. We also know that the toxicity and discontinuation rates of Zanubrutinib compare favourably with Ibrutinib in the R/R setting in the Alpine trial. It thus seems likely that this reduced toxicity will also be observed in the upfront setting compared with Ibrutinib and likely Acalabrutinib. I cannot comment on whether this will affect the calculations, but having BR as the comparator in the SEQUOIA trial should not lead to unexpected adverse events when used in the real world in the unfit population. Secondly, we are not clear why the company has chosen not to use this SEQUOIA data as evidence for the use of Zanubrutinib upfront in a "fitter" population, who currently have the unmet need in the UK of being able to access continuous, single-agent BTK therapy. If the appraisal committee were to accept that the differentiation between "fit" and "unfit" was now redundant; could they consider approving access for all?

Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL	No	The EAG rejects the company's assertion that Zanubrutinib is non-inferior to Acalabrutinib using the MAIC due to the confidence intervals observed for the hazard ratios. The CS does make some reference to this in Section B.2.1.1.2. It also sounds like this was commented on by experts in the advisory board used by the company. Even so, the pre MAIC values for OS and PFS in untreated patients are similar, suggesting that Zanubrutinib as an intervention is very similar to Acalabrutinib, even though it cannot be considered statistically non-inferior based on the MAIC. In fact, the pre-matched SEQUOIA population had more patients with disrupted p53 than the ELEVATE-TN patients so may in fact be more effective. Unable to comment as clinicians on the impact which this will have on the economic evaluation in the TA.
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL	No	Similar to Issue 2, the EAG has concerns that the SLR was insufficiently sensitive to capture all clinical studies of interest and the rationale for the actual filters chosen was unclear. In addition, the lack of more recent searches of conference abstracts beyond July 2022 was of concern and this may be more relevant for health utility values which are often published after the initial trial results and often in abstract form at conferences.
Issue 6: Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	No	As in Issue 4, the EAG rejects the company's assertion that Zanubrutinib is non-inferior to Acalabrutinib using the MAIC. Because of this, the CMA used to compare cost of the two interventions was the wrong economic evaluation, as the CMA requires robust confirmation of equivalence (non-inferiority) for both interventions. In the R/R setting in the ALPINE trial, the CS shows that Zanubrutinib confers a statistically significant 31% reduction in PFS or death at the Aug 22 data cut off when directly compared to Ibrutinib, thus confirming superiority rather than equivalence. This adds further weight to the EAG concerns in that respect

		Despite the statistical difficulties, the available data suggests that Zanubrutinib has significantly lower rates of dose-limiting toxicicty. In fit and young patients, we know that Ibrutinib is superior to both R-Bendamustine and FCR (the previous gold standard therapy) in a Phase 3 upfront setting. Given that we see reduced arrhythmic adverse effects, reduced discontinuations and improved PFS in the R/R setting with Zanubrutinib vs Ibrutinib in CLL (and in all settings in other B-cell malignancies) it seems likely that Zanubrutib will also be a superior BTKi (vs Ibrutinib) in the front-line setting and afford significant benefit to our young patients in the UK, who cannot currently access single-agent BTKi. In both settings, there is some limited real world evidence that Zanubrutinib is better tolerated even in patients who have had issues on Acalabrutinib – see ref below. Cardiovascular adverse events associated with BTKi therapy may interfere with continuation of best possible care, induce life-threatening CV complications or lead to long-term morbidity including worse CLL-related outcomes if optimal BTKi treatment is withheld. Zanubrutinib with a lower risk of development of AF and a reduced risk of sudden cardiac death (even in relation to Acalabrutinib) is likely to bring significant quality of life benefits to all BTKi eligible patients. All published studies show that Zanubrutinib is better tolerated than Ibrutinib. The impact of tolerability, and thus, the ability to maximise response, (especially to first line treatment), is difficult to assimilate into the economic evaluation over 30 years. As a clinician, it seems likely that the impact for individual patients will be significant, however, we are unable to comment of the impact of this on economic evaluation. *Real-world (RW) treatment patterns and comparative effectiveness of Bruton tyrosine kinase inhibitors (BTKi) in patients (pts) with mantle cell lymphoma (MCL).* *Bijal D. Shah, Keri Yang, Andrew J. Klink, Tom Liu, Todd M. Zimmerman, Ajeet Gajra, and Boxiong Tang* *Journal of Clinical Oncology 2022 40:16_suppl, e18727-e18727*

Issue 7: Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	No	The EAG criticises the CS as it does not use utility values collected from the compared trials; rather, the company used values from an UK general age-sex matched population, and does not address the uncertainty in these values. The EAG went on to explore scenarios using actual utility values from the SEQUOIA and ALPINE trials and found that because of the cost savings with Zanubrutinib, changes to utility values had a minimal effect on overall conclusions. So it appears that Issue 7 is unlikely to impact on the outcome of the TA.
Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	No	The effectiveness of Zanubrutinib means that within the time frame of the trial so far reported (<30.5 months), there are few progression events or deaths. This means that the survival curves for the 30 year horizon for the evaluation must be based on parametric models. There are a wide variety of these. The EAG would have preferred more exploration of various models in the CS. The company did apply alternative survival curves to PFS and OS as part of their scenario analyses only and the EAG conducted further scenario analyses not modelled by the company. Alternative models did change the incremental results for costs and QALYs but did not alter overall conclusions. It would seem sensible to collect real world data to inform the accuracy of these models and perhaps help in future appraisals.
Issue 9: Uncertainty in untreated “high-risk” CLL subgroup	Yes	The NICE scope for this TA required data from subgroup analyses for those with p53 disruption in the untreated population. In this population in the UK, both Ibrutinib and Acalabrutinib are available. The SEQUOIA trial recruited patients with TP53 disruption (n=110) into a separate cohort who all received Zanubrutinib. At a median follow-up of 27.7 months, PFS was not reached. For Ibrutinib, the company used data from the ALPINE trial which is a direct comparison between the 2 drugs, but was conducted in the R/R population. Patients with p53 disruption in the R/R setting do not have the same genetic profile as patients with p53 disruption in the untreated setting.

		For Acalabrutinib, the CS focused on the 2020 Sharman Lancet publication on ELEVATE-TN, which does not contain any data on the relevant subgroups. In a more recent letter with a median follow-up of 46.9 months for the same trial, median PFS was not reached in the acalabrutinib-containing arms in patients with del17p and/or mutated *TP53* (n=82). Demographic data on the characteristics of this subgroup was not published. Thus, data is limited and direct comparisons impossible. Real world data and longer term follow-up will inform some comparisons but this will take years. Ref: Sharman, J.P., Egyed, M., Jurczak, W. *et al.* Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia* 36, 1171–1175 (2022)

Additional issues

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Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Janssen-Cilag Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	NA

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL	Yes/No	NA
Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL	Yes/No	NA
Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison	Yes/No	SEQUOIA trial compares zanubrutinib with bendamustine + rituximab (BR) to determine its effectiveness as frontline therapy in patients with chronic lymphocytic leukaemia (CLL). BR is known to be more toxic than chlorambucil + obinutuzumab (O-Clb). Therefore, patient selection in SEQUOIA might have been impacted to ensure that if a patient is randomised to the BR arm, the patient would be fit enough to tolerate this treatment. This would imply that patients in the SEQUOIA trial might likely have been fitter than patients who would otherwise receive O-Clb. This may have implications on contextualizing the relative efficacy, and especially safety of Zanubrutinib when compared to other regimens (e.g. acalabrutinib and ibrutinib) as the trials (e.g. ELEVATE-TN and GLOW) include patients who could

<table>
<tr><td></td><td></td><td>have been randomised to O-Clb, and therefore are likely to be less fit compared to those in the SEQUOIA trial.</td></tr>
<tr><td>Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL</td><td>Yes/No</td><td>There was no matched-adjusted indirect comparison (MAIC) undertaken to inform the relative efficacy of Zanubrutinib vs ibrutinib. The ALPINE trial was used to inform the comparative efficacy instead.
In the zanubrutinib submission, the ALPINE trial results are used to argue that ibrutinib has at least similar efficacy or is less effective given statistically significant results for independent review committee (IRC) progression-free survival (PFS) and there is no statistical difference in overall survival (OS).
Janssen would position that ibrutinib being 'less effective' than zanubrutinib is very unlikely:
1. The appendix of Brown et al. 2023 manuscript shows that both investigator-assessed (INV) and IRC PFS show no statistically significant difference between zanubrutinib and ibrutinib in the Europe subgroup [hazard ratio (HR) of 0.72, 95% confidence interval (CI) 0.51-1.03 vs 0.75, 95% confidence interval (CI) 0.53-1.07]. It is noted that the statistically significant difference is observed in North America and Asia regions.
2. This EHA abstract outlines the oddly weak performance of Ibrutinib in the ALPINE trial. The efficacy results in the ALPINE study for Ibrutinib are not consistent with data seen in other phase 3 relapsed/refractory (RR) setting. Phase 3 RESONATE study which included heavily pre-treated higher risk patients showed similar PFS data during the first year to ALPINE (Table 1).
Table 1: Ibrutinib median PFS from different RR CLL studies
<table>
<tr><th>Ibrutinib arm from different RR CLL studies</th><th>Median prior lines of treatment</th><th>High-risk TP53 aberrated patients</th><th>Ibrutinib median PFS</th></tr>
<tr><td>ALPINE</td><td>1</td><td>23%</td><td>35 months</td></tr>
<tr><td>ELEVATE RR</td><td>2</td><td>45%</td><td>38 months</td></tr>
<tr><td>RESONATE</td><td>3</td><td>30%</td><td>44 months</td></tr>
</table>
</td></tr>
</table>

		Additionally, both regimens in the ALPINE trial are oral and a double-blind design would have been feasible with no ethical concerns (unlike when comparing to an intravenous regimen).
Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL	Yes/No	NA
Issue 6: Use of a cost-minimisation analysis as the company's base-case in untreated CLL and R/R CLL	Yes/No	NA
Issue 7: Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	Yes/No	NA
Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	Yes/No	NA
Issue 9: Uncertainty in untreated "high-risk" CLL subgroup	Yes/No	NA

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Silvy Mardiguian, Market Access Director, UK & Ireland
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	BeiGene UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	Submitting Company
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

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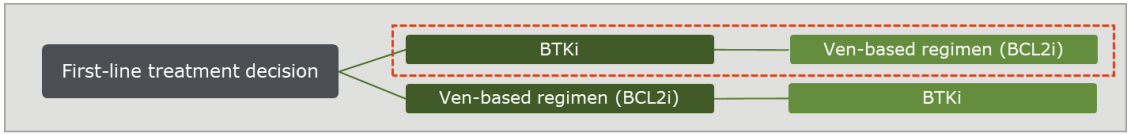
Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Exclusion of venetoclax-rituximab as an eligible comparator in R/R CLL	No	The Company does not consider venetoclax-rituximab to be a comparator to zanubrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) and so believe that the exclusion of venetoclax-rituximab is justified. A 'sequencing' approach is recommended in the 2022 British Society for Haematology (BSH) guidelines when selecting the optimal strategy for patients who have relapsed following treatment with front-line targeted agents.[1] Treatment sequencing suggests that the optimal treatment following progression varies depending on the front-line therapy (as per Figure 1 below): • For patients progressing following front-line treatment with a Bruton tyrosine kinase inhibitor (BTKi), a B-cell lymphoma 2 inhibitor (BCL2i) regimen is recommended. • For patients progressing following front-line treatment with a BCL2i, a BTKi regimen is recommended.

Figure 1: Treatment decision as per BSH guidelines



The introduction of zanubrutinib will 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 patients with R/R CLL. Whilst venetoclax-rituximab is recommended by the National Institute for Health and Care Excellence (NICE) for patients with R/R CLL irrespective of which prior therapy was received, as noted in the 2022 BSH guidelines there is a distinct lack of data on rechallenging patients with a venetoclax-based regimen.[1] Venetoclax-rituximab is primarily used in patients previously treated with a BTKi.[2]

The Company acknowledges that a small proportion of patients who are treated with front-line chemo-immunotherapy (CIT) may receive second-line venetoclax-rituximab. However, the introduction of targeted pathway inhibitors has represented a paradigm shift in front-line treatment, challenging the role of CIT.[1] This was confirmed by UK experts at an advisory board (3rd November 2022) who emphasised that CIT usage has declined in the first-line setting since the availability of targeted therapies. This conclusion was also reiterated by the submitting Company of NICE ID 3860, who noted that *'the role of CIT in first-line treatment has diminished following the approval of targeted pathway inhibitors in recent years'*.[3,4] As the use of CIT continues to decrease, the pathway for patients will continue moving towards a BTKI/BCL2i sequencing approach, as recommended in the BSH guidelines.[1]

In addition, based on UK prescribing data, only [redacted]% of patients received second-line treatment with venetoclax-rituximab, whereas [redacted]% of patients received second-line treatment with a BTKi. This is likely due to the intensive dosing regimen of venetoclax-rituximab and the associated risk of tumour lysis syndrome. In comparison, [redacted] of patients received third-line treatment with a venetoclax-based therapy, whereas only [redacted]%

		of patients received third-line treatment with a BTKi. This indicates that the treatment sequencing algorithm in patients not treated with a BTKi in the first-line is to receive a BTKi in second-line and a BCL2i in third-line. Patients eligible for zanubrutinib are those who have not previously received treatment with a BTKi (aligned with the inclusion/exclusion criteria of the ALPINE trial), and therefore, venetoclax-rituximab is not a relevant comparator for zanubrutinib.[5] This was confirmed by feedback received from five UK clinicians, gathered in double-blinded, 1:1 interviews conducted by the Company.[3] Furthermore, feedback gathered from UK experts at an advisory board (3rd November 2022) conducted by the Company supported the sequencing concept and the positioning of zanubrutinib as an alternative BTKi treatment option in this patient population.[6] The Company would also like to reemphasise that the network meta-analysis (NMA) analysis (versus venetoclax-rituximab) conducted by the Evidence Assessment Group (EAG) is subject to substantial uncertainty as noted in the Company response to the EAR and in the limitations noted by the EAG regarding their methodology. As such, the NMA analysis is unsuitable for use to inform decision-making.
EAG Response	The Company have not supplied any new evidence for the EAG to critique to support their response to Key Issue 1. The EAG maintains its statement from the FAC that they cannot comment on the IQVIA data as they do not have access to this data in individual or summary form. As previously stated in the FAC, based on the Company's quantitative survey data provided to the EAG by the Company in their response to the clarification letter,[1] the clinicians surveyed report treating [redacted] of R/R CLL patients with VenR, which the EAG does not consider to be a small proportion of patients given that [redacted] were treated with a BTKi. In addition, [redacted] The EAG considers that a significant minority of patients receiving VenR as a second line therapy and, therefore, VenR would have been an appropriate comparator within the submission. As mentioned by the Company above, the EAG conducted a NMA and acknowledged the uncertainty in the results within the EAG Report (Section 3.5.1). The EAG would like to reiterate that the purpose of the NMA was to illustrate the plausibility of a network between zanubrutinib and VenR and not to draw any conclusions based on these results due to the uncertainty in the derived estimates. The EAG's position on the	

	interpretation of the NMA results was made clear in the EAG report, Section 1.2: "The EAG undertook an NMA using the data from the SLR and TA561 to generate effectiveness estimates for VenR. The results were: PFS HR = 1.48 (95% CI 0.49, 4.45); and OS HR = 1.87 (95% CI 0.59, 5.91). Based on the point estimates, VenR is more effective than zanubrutinib but, given the wide confidence intervals, the EAG cannot draw firm conclusions on the effectiveness and hence cost-effectiveness of VenR. This limitation is compounded because the EAG have concerns that the search strategy used to identify evidence for VenR may not be sufficient". Furthermore, the effect of including VenR as a comparator in the R/R CLL model on the cost-effectiveness of zanubrutinib was not estimated by the EAG due to the uncertainty in the effectiveness estimate derived by the EAG. The EAG maintain their previous stance on the illustrative use of the NMA.

Issue 2: Uncertainty in the sensitivity of the systematic literature review to capture all clinical studies of interest in untreated CLL and R/R CLL	No	The Company conducted a robust clinical systematic literature review (SLR) using the Embase interface (via Embase.com), an interface which is commonly used in conducting SLRs forming evidence submissions to NICE and considered to be a core database for literature searching in the NICE literature searching and evidence submission guidelines.[7–11] The Embase interface searches Embase, EMBASE classic and MEDLINE databases simultaneously using one search strategy and as such, there is no need to use separate search strategies to search the individual databases. The search terms are translatable to other interfaces, such as Ovid, meaning that the EAG would be able to test the search strategies within the databases they have access to, if required. All relevant literature for previously untreated and R/R CLL were retrieved through the appropriate search terms. The EAG were not able to identify additional publications that were missed within the database searches or note any additional publications that would be relevant to decision making. Follow-up interviews with two leading UK clinical experts confirmed that all key studies relevant for decision-making were captured in the SLR.[12] When comparing to the ibrutinib-venetoclax appraisal (TA10746), no additional publications were identified in this appraisal compared to the Company's appraisal. The literature used to inform the matching adjusted indirect comparison (MAIC) conducted versus acalabrutinib (ELEVATE-TN) in TA10746 was in line with the literature the Company used for their MAIC analysis versus acalabrutinib as reported in the CS.[13] Both appraisals have used Sharman *et al.* (2020) as a data source for ELEVATE-TN.[14]

		Relevant conference and abstract proceedings were captured in the SLR, and the amendments made to the Scottish Intercollegiate Guidelines Network (SIGN) filters would not impact the ability of the filter to capture relevant studies as the edits made were to widen the filters to capture conference abstracts and proceedings (which the filter previously omitted). Both branded and generic drug names were included in the search terms for the intervention and comparator. Exploded search terms were used for the generic drug names meaning any words or phrases associated with the names would have been captured. Therefore, it is highly unlikely that any key publications were missed. Additionally, grey literature searches or 'hand-searches' were conducted by the Company to identify any additional conference abstracts that the Embase interface may have missed – these searches did not identify any additional publications. The Company would also like to outline that conference abstracts would unlikely contain sufficient information to impact decision-making. As MAICs are required to adjust for heterogeneity, data on aggregate cohort characteristics would be required, which are rarely reported within a conference abstract. Whilst the Company appreciates that the SLR was now conducted 9 months ago given the timelines associated with the NICE process, the Company would like to reiterate that the SLR was conducted in line with NICE requirements and was conducted within 6 months of submission as per the NICE methods guide.[15] The EAG recognised that this is a **common** concern of the Health Technology Assessment (HTA) process and its variable timelines, therefore reducing the severity of the concern over the timelines of the Company's SLR. In addition, the Company's medical team regularly keep up to date with new publications that could be relevant for use in the submission and no additional publications have been identified by them. The Company conducted additional searches in nonbibliographic databases including the NICE and Scottish Medicine Consortium (SMC) websites using alternative spelling and search terms without identifying any additional key publications that would be relevant to the appraisal.

		The methods used by the Company for the SLR are aligned with previous NICE appraisals and follow the NICE methods guide.[15] The Company believes that the EAG's concern over the methods have **no** material impact on decision-making ability.
EAG response	The EAG would like to note that new information has been presented by the Company for Issue 2, "Follow-up interviews with two leading UK clinical experts confirmed that all key studies relevant for decision-making were captured in the SLR." The EAG were not privy to any follow-up discussions the Company had with Clinical Experts and these discussions were not reported by the Company in the Points for Clarification or Factual Accuracy Check hence the EAG is unable to verify this evidence. The EAG would like to clarify that the function of the EAG within a Technical Appraisal is to offer the Company a professional critique of the search strategy and signpost any issues that may affect the evidence identification process. It is not within the remit of the EAG, and they are not responsible for re-running any searches, undertaking any new searches, or reporting any potentially relevant publications missed by the Company. The EAG acknowledge that searches may be translated to another interface, however, as stated the function of the EAG is to evaluate the search strategy presented and not run the search in another interface, such as OVID, as this would not resolve any interface-related concerns. The Company advise that no additional publications were sourced through grey literature or hand-searching. Within the Points for Clarification, the EAG requested the search strategies for any grey literature or hand-searches conducted by the Company to offer methodological critique. As the Company have not provided this information, the EAG cannot verify their assertion that no key publications were missed and maintain their position. Though the Company indicate conference abstracts would not contain decision-making information, they are still an important aspect of searching as they may indicate relevant trials, research, or evidence in the field that would impact decision-making. The Company reports conducting searches in non-bibliographic databases and utilising alternative spelling and search terms. These were not included in the search strategies provided by the Company, either in the original submission or when the EAG requested these in the Points for Clarification. The EAG are therefore unable to verify the Company's assertion that no additional relevant publications were identified and maintains its concerns over alternative spelling searches.	

	The Company assert they followed the NICE methods guide but the EAG are unable to support this statement. As per section 3.3.25 of the guide,[2] the Company have not transparently reported all unpublished and part-published evidence. Such evidence should also undergo the same critical appraisal as the bibliographic search.

Issue 3: Applicability of the SEQUOIA trial population to the untreated CLL comparison	No	**<u>Trial designs and eligibility</u>** The Company agrees with the EAG's conclusion that the definition of patient fitness is non-binary, driven by mainly patient characteristics as opposed to treatment eligibility (as confirmed by UK clinical experts [please refer to section below Table 1]).[12] In addition, clinical experts confirmed that the definition of 'fitness' is subjective and becoming less relevant in driving treatment decisions given the declining usage of CIT. Hence, it is important to compare trial design, and patient eligibility across relevant front-line trials in CLL to demonstrate that SEQUOIA is appropriate for decision-making in previously untreated patients with CLL. Key eligibility criteria and patient characteristics of SEQUOIA, ELEVATE-TN and CLL10 are presented in Table 1. The SEQUOIA trial is overall more akin to the eligibility criteria and patients characteristics for the ELEVATE-TN trial which was deemed representative of the previously untreated "unfit" patients with CLL by NICE.[16,17] In comparison, there is a difference in the key eligibility criteria for CLL10 which was deemed representative of the previously untreated "fit" patients with CLL by NICE.[18] The key differences between the inclusion criteria of the CLL10 trial and the SEQUOIA trial are age, Cumulative Illness Rating Scale (CIRS) score and creatine clearance level. The only key difference between the eligibility criteria of the SEQUOIA trial and the ELEVATE-TN trial is that patients in the SEQUOIA trial were eligible for treatment with bendamustine-rituximab whereas patients in the ELEVATE-TN trial were not eligible for treatment with bendamustine-rituximab. Bendamustine-rituximab was used as a comparator in the SEQUOIA trial because at the time of study design, the standard front-line treatment in patients without 17p deletion or TP53 mutation was CIT. Bendamustine-rituximab was a commonly used standard treatment option for front-line "unfit" CLL patients without 17p deletion in the countries in which the trial was to be conducted.[19,20]

In the UK, bendamustine-rituximab was recommended as an alternative treatment option for less "fit" patients with CLL by the BSH in their 2018 guidelines,[21] but has since been removed in the most recent 2022 guidelines following the introduction of targeted therapies. The choice of bendamustine-rituximab was agreed upon as a globally acceptable comparator with regulatory authorities, including the Food and Drug Administration (FDA) and European Medicines Association (EMA).

The EAG acknowledge that the SEQUOIA trial recruited patients who were not "fit" for intensive CIT (e.g. fludarabine-cyclophosphamide-rituximab), however were suitable to receive treatment with bendamustine-rituximab. Therefore, the SEQUOIA trial bridges the gap between the CLL10 trial (suitable for either fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab) and the ELEVATE-TN trial (not suitable for either fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab). This was supported by UK clinical experts who described patients in ELEVATE-TN and SEQUOIA as 'no go patients' and 'slow go patients' for CIT, respectively.[12] This overlap in eligibility criteria, allows clinical data from SEQUOIA to be comparable to ELEVATE-TN, to allow for a robust MAIC of zanubrutinib versus acalabrutinib in the "unfit" patient population. At the same time, the fact that patients could tolerate bendamustine-rituximab in SEQUOIA means there is also overlap with patients in the CLL10 trial. Overall the Company consider that the SEQUOIA trial is appropriate for decision-making for the previously untreated CLL patient population irrespective of fitness levels.

Table 1: Key inclusion criteria of CLL trials

Characteristic	CLL10[18]	SEQUOIA (Cohort 1)[17]	ELEVATE-TN[16]
Interventions	FCR (n=282) BR (n=279)	Zanubrutinib (n=241) BR (n=238)	Acalabrutinib-obinutuzumab (n=179) Acalabrutinib (n=179) Chlorambucil-obinutuzumab (n=177)
Trial design	Phase III, open-label	Phase III, open-label	Phase III, open-label
Age	Aged ≥18	Aged ≥65 years, or 18 - 64 years if presenting with more	Aged ≥65 years, or 18 - 64 years if presenting with more

		severe disease as defined by CIRS score, creatinine clearance or infection history	severe disease as defined by CIRS score and creatinine clearance
FCR/BR eligibility	FCR, BR eligible	FCR ineligible, BR eligible	FCR, BR ineligible
Key inclusion criteria	Patients must meet all criteria: **Age:** ≥18 years **CIRS:** ≤6 **Creatinine clearance:** ≥70 mL/min **Other:** -	Patients must meet at least **one** of the following criteria: **Age:** ≥65 years **CIRS:** >6 **Creatinine clearance:** <70 mL/min **Other:** History of severe or frequent infections	Patients must meet at least **one** of the following criteria: **Age:** ≥65 years **CIRS:** >6 **Creatinine clearance:** <70 mL/min **Other:** -
ECOG PS	0 – 2	0 – 2	0 - 2
Key exclusion criteria	Detection of del(17p)	Detection of del(17p)	-

BR – Bendamustine-rituximab; CIRS – Cumulative Illness Rating Scale; del(17P) – Deletion of the short arm chromosome 17; ECOG PS - Eastern Cooperative Oncology Group Performance Score; FCR – Fludarabine-cyclophosphamide-rituximab; min – Minute; mL – Millilitre.

Clinical validation

Follow-up interviews with two leading UK clinical experts practicing in CLL held via a teleconference (27th April 2023) conducted by the Company confirmed that in current clinical practice, BR would not be considered as an appropriate treatment option for the patient population of the SEQUOIA trial based on current guidelines.[12] They stated that the comparator arm is irrelevant to decision-making given that the treatment guidelines have changed since enrolment for the SEQUOIA trial following the introduction of newer targeted therapies (first patient randomised in SEQUOIA on 31th October 2017 whereas BR was removed as a recommendation for less “fit” patients with CLL from the UK BSH guidelines in 2022).[1,17] They noted that consideration of clinical characteristics is more

		important in determining fitness, with both clinicians agreeing that the inclusion criteria of the SEQUOIA trial and the ELEVATE-TN trial are aligned. Moreover, the clinical experts highlighted that treatment eligibility should not be used to define fitness of patients as eligibility for treatments changes over time based on treatment guidelines and there is currently crossover in eligibility for treatments based on previous definitions. They also noted that, given that most patients can tolerate targeted therapies now (whether above or below 65 years old), classifying patients by 'fitness' status is becoming less relevant in driving treatment decisions. **<u>Regulatory support</u>** The European approval of zanubrutinib by the EMA confirms the applicability of the SEQUOIA patient population to the previously untreated "unfit" population: *"Despite inclusion exclusion criteria of study 304 [SEQUOIA] in the frontline setting clearly indicate that patients should have been unsuitable for treatment [with] chemoimmunotherapy (FCR), study 305 [ALPINE] showed noninferiority and superiority (based on INV assessment) against ibrutinib in the R/R setting. Having in mind that ibrutinib is also approved in 1L, and recommended in both fit and unfit patients, it seems justified to extrapolate the use of zanubrutinib to 1L fit patients. Thus, despite the limitations of study 304 and the comparison against BR in an elderly and unfit population, the totality of evidence supports the use of zanubrutinib in both fit and unfit patients."*[22]
EAG response	The Company have provided further information to support their claim that eligibility for bendamustine-rituximab (BR) should not be considered, only clinical fitness should be considered when defining "fitness" in this response. This additional information is from a teleconference the Company had with two UK-based Clinical Experts practicing in CLL held on 27 April 2023. The response from these Clinical Experts acknowledges that BR is no longer a recommended treatment option according to the most current BSH guidelines,[3] and that clinical characteristics are more important in determining "fitness". As the EAG have not seen transcripts or summaries of the discussions held with these experts on 27 April 2023, we cannot comment further on the additional information that has been provided by the company.	

	As stated in the FACs and as agreed by the Company in their response, the EAG acknowledge the ambiguity in defining "fitness". The Company have provided additional information on whether participants in the CLL10 and ELEVATE-TN trials were eligible or ineligible for BR and FCR to help position the population of SEQOUIA participants compared to other trials in CLL. However, the issue the EAG is highlighting is the uncertainty caused by the definition of "fitness" in the CS. This potentially creates uncertainty in the generalisability of the SEQUOIA trial to a UK population as these patients were considered “fit” for BR, which is a CIT. This uncertainty is described in further detail in Section 2.5 of the EAG Report.

Issue 4: Uncertainty in the interpretation of MAIC results for survival outcomes in untreated CLL and R/R CLL **Issue 6:** Use of a cost-minimisation analysis as the company’s base case in untreated CLL and R/R CLL **Issue 9:** Uncertainty in untreated “high-risk” CLL subgroup	No	A comprehensive SLR was conducted to identify the most appropriate evidence to inform the efficacy of zanubrutinib, acalabrutinib and ibrutinib. Three MAICs were conducted comparing zanubrutinib with acalabrutinib in patients with previously untreated and R/R CLL. The MAICs were conducted in line with NICE recommended methodology and made best use of the available evidence for zanubrutinib and acalabrutinib.[23] Whilst the MAICs did not demonstrate a statistically significant difference in progression-free survival (PFS), all MAICs demonstrated a numerical improvement in PFS for zanubrutinib compared to acalabrutinib. To alleviate uncertainty in the MAIC estimates and align with previous appraisals in CLL, the Company took the conservative approach to assume equal efficacy and safety within a cost-minimisation analysis (CMA) approach despite demonstrating improved PFS in all MAIC models.[16] There is a paucity of evidence specifically reported in patients with 17p deletion and/or TP53 mutation for alternative BTKis and no studies were identified in the SLR which reported outcomes and baseline characteristics for this patient population. Cohort 2 of SEQUOIA is among the largest bodies of prospective evidence collected specifically for patients with a 17p deletion and demonstrated consistent outcomes to treatment with zanubrutinib in patients without 17p deletion (comparable to outcomes of arm A in Cohort 1). The issue of a lack of data in “high-risk” CLL has been evident across several previous appraisals in patients with previously untreated CLL. In NICE TA689 and TA429, it was agreed that data from the R/R setting is an appropriate proxy to inform the clinical

		effectiveness of two BTKis (acalabrutinib and ibrutinib) in patients with previously untreated "high-risk" population.[24,25] The ALPINE trial showed clinical superiority of zanubrutinib over ibrutinib in the R/R setting, and a statistically significant improvement in PFS versus ibrutinib in patients with "high-risk" R/R CLL. Since the ELEVATE-RR trial showed acalabrutinib to be non-inferior to ibrutinib, it follows that it is plausible to assume that zanubrutinib is at least clinically equivalent to acalabrutinib and ibrutinib. The assumption of equal efficacy in patients with previously untreated "high-risk" CLL was validated with UK clinical experts in attendance at an advisory board (3rd November 2022) and follow-up interviews with two UK clinical experts who deemed the conclusion that the treatment effect of zanubrutinib is at least equivalent compared to alternative BTKis as clinically plausible.[6,12] The Company have also presented additional analyses to support the efficacy of zanubrutinib in patients with previously untreated "high-risk" CLL. This included a MAIC comparing zanubrutinib with acalabrutinib in a previously untreated (unfit and "high-risk") patients (using ELEVATE-TN) and a MAIC comparing zanubrutinib with acalabrutinib in patients with "high-risk" R/R CLL (using ELEVATE-RR), both demonstrating that PFS and overall survival (OS) between acalabrutinib and zanubrutinib is not statistically significantly different, irrespective of patient's mutational status. Furthermore, a naïve comparison was conducted with ibrutinib using Mato et al (2018), which was the only ibrutinib study identified for the "high-risk" population during the clinical SLR. The naïve comparison demonstrated that there was no statistically significant difference in PFS between zanubrutinib and ibrutinib. However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib, in favour of zanubrutinib. Interviews with two UK clinical experts confirmed that the Mato et al publication provides useful evidence for ibrutinib to use in a naïve comparison and that this should be sufficient to demonstrate that there is at least equal efficacy between zanubrutinib and other BTKis in patients with previously untreated "high-risk" CLL.[12] As recommended in the NICE methods guide, a CMA approach "*can be used when the health effects of an intervention are the same as those of the status quo"*.[15] In TA689, the submitting Company undertook an unanchored MAIC to compare acalabrutinib with

		ibrutinib in patients with previously treated R/R CLL. A statistically significant difference was not demonstrated for PFS or OS between the two treatments, resulting in the submitting Company concluding that the results of the MAIC demonstrate that the efficacy of acalabrutinib in PFS and OS in patients with R/R CLL is at least equivalent to that of ibrutinib. The EAG concluded that it was reasonable to assume clinical equivalence of acalabrutinib and ibrutinib in patients with previously treated R/R CLL. Results from the MAIC were used to justify the use of a CMA approach for decision making and this approach was accepted by the Committee. Zanubrutinib is a next-generation BTKi and results of the ALPINE trial, MAICs and clinical expert opinion support the plausible equivalence of zanubrutinib compared to alternative BTKis. The Company acknowledges that there is uncertainty associated with the cost-minimisation approach. However, the models were built as a cost-utility model and include all the appropriate functionality to conduct a cost-utility analysis. For the Company base case, a cost-minimisation approach was adopted by assuming equivalent efficacy and safety profile for all treatments. In all scenarios conducted by both the Company and the EAG in which a cost-utility approach was adopted, zanubrutinib remained below NICE's willingness-to-pay threshold with results consistent when tested both deterministically and probabilistically. By varying the MAIC hazard ratios (HRs) in accordance with the uncertainty of the respective distributions, the probabilistic analysis accounts for the uncertainty in the HRs between zanubrutinib and acalabrutinib and between zanubrutinib and ibrutinib. As outcomes still favoured zanubrutinib when run probabilistically, it is plausible to assume that zanubrutinib is at least clinically equivalent to acalabrutinib and ibrutinib and a cost-minimisation approach is justified.
EAG response	The EAG has acknowledged that evidence from the ALPINE trial suggests that assuming equivalent clinical effectiveness between ibrutinib and zanubrutinib in R/R CLL patients is a conservative assumption against zanubrutinib. However, the two MAICs used to compare acalabrutinib with zanubrutinib in R/R CLL patients reported two different point estimates of relative effectiveness and wide confidence intervals. Following these results, the EAG considers that, although one might assume equivalent clinical effectiveness with	

	acalabrutinib in R/R CLL, the upper limit of the 95% CI includes a clinically important difference, hence a CUA would have been a more accurate representation of the uncertainties in the decision problem. For untreated CLL, the absence of comparative evidence between zanubrutinib and acalabrutinib meant that data from "unfit" patients had to be pooled with "high-risk" patients to produce the evidence for "unfit" patients. Similarly, the MAIC for "high-risk" patients utilises data from R/R CLL patients from ALPINE and ELEVATE-RR to assess the relative effectiveness of zanubrutinib versus acalabrutinib. As a result, both analyses led to effectiveness estimates with wide confidence intervals have include clinically important differences. Hence a conclusion of equivalent clinical effectiveness cannot be made for these comparisons. Following these analyses, the key concern for the EAG is the absence of a discussion by the Company on whether the confidence intervals around the relative effectiveness estimates include a clinically meaningful difference such that zanubrutinib would be considered inferior to its comparators. It is likely that clinical advisers are willing to accept a low level of risk based on the point estimates but given the width of these estimates and the value of the upper 95% CI limit, there is a potentially a higher level of risk associated with zanubrutinib in these comparisons. Therefore, the EAG maintains its position that the main MAIC results show an absence of evidence of no difference, rather than demonstrating no difference in effectiveness between zanubrutinib and acalabrutinib. Hence, the conditions required for the adoption of a CMA approach have not been met and a CUA would have been more appropriate. A CUA approach would have facilitated the incorporation of the uncertainty in these effectiveness estimates into the economic analysis and supported an assessment of how likely zanubrutinib would be cost-effective compared with and acalabrutinib. At present a judgement would be needed as to whether or not incorporating this imprecision is material but that judgement is constrained by an information gap which could have been addressed. The Company state above that the EAG in TA689 were willing to accept clinical equivalence when a statistically significant improvement was not observed.[4] However, given that these values are redacted, it is not clear to the EAG whether the 95% CIs included a clinically meaningful difference in effectiveness outcomes. The EAG acknowledges that external evidence for studies such as Mato *et al*. (2018)[5] are useful. However, as mentioned in the EAG report, these results must be read with caution as there are differences between

	the populations and methodologies that are not being controlled for and which potentially introduces a risk of bias. The EAG also acknowledges that the two models submitted by the Company allowed for scenarios using a CUA rather than a CMA. However, the EAG expressed concerns that the semi-Markov model structure adopted by the Company for the untreated CLL population may not have been appropriate for a CUA (Section 4.3.2). In addition, while the EAG recognise there is limited longer-term data available to inform the economic models (Key Issue 8), the EAG had concerns that the assumptions made by the Company to inform the CUA did not utilise all of the available data. Therefore, the EAG made alternative assumptions in the EAG basecase analysis (Section 6.2.1.2). Whilst the results from the EAG basecase and scenario analyses were favourable for zanubrutinib, the EAG still considers there to be uncertainty in these conclusions as strong assumptions were made by the EAG. It is also worth highlighting that, while the PSA captures parameter uncertainty, further structural uncertainties (e.g. the long term effectiveness of zanubrutinib in NHS patients, particularly in terms of OS and HRQoL,[6] or differences in the methodologies, data collection, and population characteristics across the trials informing the MAICs) may not have been accounted within the CUA model presented by the Company.

Issue 5: Uncertainty in the sensitivity of the systematic literature review to capture all potentially relevant studies reporting utility values in untreated CLL and R/R CLL **Issue 7:** Uncertainty in the utility estimates used in the company economic model in untreated CLL and R/R CLL	Yes	The Company are confident that the SLR captured all relevant studies reporting utility values given that the methods used were in line with the NICE literature searching and evidence submission guidelines.[7–11] Details on the time frame in which the SLR was conducted and the search strategy are included in Issue 2. The EAG recognised that filter adaptation is not unusual and therefore alleviating the concern around the health state utility value filter being adapted for use in Embase.com. As a CMA has been used in the Company base case, the choice of utility values will not affect the cost-minimisation estimates. However, to alleviate the concerns of the EAG and assess the impact of alternative utility values on cost-effectiveness, the Company has reviewed previous utility values accepted by NICE in past CLL appraisals. The alternate utility values the Company explored are presented in Table 2 and Table 3 for the untreated and R/R CLL populations, respectively.

In all recent appraisals for both previously untreated and R/R CLL, the PD utility of 0.6 has been deemed appropriate as derived from Holzner *et al.* (2004).[2,13,26–28] Various scenarios using the PD utility values from ALPINE or SEQUOIA, or any decrements due to progression derived from the trial data are not deemed relevant, given that the PD trial utility values lacked face validity. Hence the Company deem it appropriate to maintain the value of 0.6 for the PD utility value. On the other hand, the progression-free (PF) utility has varied across appraisals. The PF utility value used in the base-case analysis for the untreated model was similar to that reported in TA689, however, a lower value was reported in TA663 and GID-TA10746. The PF utility value used in the base-case analysis for the R/R model was the same as that reported in TA561, whereas TA689 used a higher utility for this health state.

As presented in Table 2 and Table 3, the use of alternative utilities that have been considered suitable by NICE Committees for decision-making does not affect the conclusions of the cost-utility analyses (CUAs) where zanubrutinib remained cost-effective in all scenarios. This is consistent with the EAG's conclusion, that across all scenarios conducted by the EAG and Company, zanubrutinib remained the preferred treatment compared with acalabrutinib and ibrutinib. Hence, the Company do not believe that use of additional alternative utility values would have an impact on the conclusions drawn from the cost-effectiveness model.

Table 2: Utility scenarios in previously untreated model (CUAs)

Source	Health state	Utility	ICER vs Ibrutinib	ICER vs acalabrutinib
Company utility values	PF	0.783	Dominant	Dominant
	PD	0.600		
TA689[25]	PF	0.780*	Dominant	Dominant
	PD	0.600		
TA663[29]	PF	0.670	Dominant	Dominant
	PD	0.600		
GID-TA10746[4]	PF	0.670	Dominant	Dominant
	PD	0.600		

ICER – Incremental cost-effectiveness ratio; PD – Progressed disease; PF – Progression free; vs – versus; SW – Southwest. **Note.** An ICER in the SW quadrant needs to be greater than the willingness-to-pay

threshold to be considered cost-effective. *In instances where data has been marked up for the base case used in the appraisal, the utilities provided as a scenario by the EAG have been used.

Table 3: Utility scenarios in R/R model (CUAs)

Source		Utility	ICER vs Ibrutinib	ICER vs acalabrutinib (ICER)
Company utility values	PF	0.7480	Dominant	Less costly and less effective [redacted]
	PD	0.6000		
TA689	PF	0.7800*	Dominant	Less costly and less effective [redacted]
	PD	0.6000		
TA561	PF	0.7480	Dominant	Less costly and less effective [redacted]
	PD	0.6000		

ICER – Incremental cost-effectiveness ratio; PD – Progressed disease; PF – Progression free; vs – versus; SW – Southwest; R/R – relapsed/refractory. **Note.** An ICER in the SW quadrant needs to be greater than the willingness-to-pay threshold to be considered cost-effective. *In instances where data has been marked up for the base case used in the appraisal, the utilities provided as a scenario by the EAG have been used.

EAG response:

The EAG would like to clarify that we do not support the statement the Company has made about filter adaptations. The EAG report highlighted the manipulation of a validated filter as an issue that should be reported for transparency and that might have implications for the search (Table 1.6, Key issue 5). Filter translation for adaptation to different search platforms and databases from the original database in which it has been created and validated is common and necessary; this is usually undertaken by an information specialist with skills and knowledge in controlled vocabulary terms and search fields of the databases involved in the translation. The Company provided no information about the process followed and, therefore, the EAG maintains its concerns raised about this filter manipulation.

The Company has presented new evidence and the EAG has assumed that this new evidence was arrived at by means of recent searches which have not been reported. Therefore, the EAG cannot comment on the quality of these searches. The originally reported search for 'CLL' undertaken in the NICE website (https://www.nice.org.uk/) and included in the CS, Appendix D, Table 6 for grey literature searches (11th August 2022) could not have identified GID-TA10746. However, a search on https://www.nice.org.uk/ for

	'Chronic Lymphocytic Leukaemia' retrieves 51 results (as opposed to 6 when searching for 'CLL' as reported in Table 6 Appendix D of the CS). Amongst those 51 results is the GID-TA10746, which the Company is now using to update the utility scenarios. This is a practical illustration of why using alternative word spellings and expanding acronyms is not only recommended but required for a robust methodology that allows for the identification of relevant evidence and supports the EAG's Key Issue that there is uncertainty in the sensitivity of the systematic review to capture utility data. The EAG has noted that although Holzner *et al* (2004)[7] was previously accepted by NICE,[4] there are concerns in the methodology used within the study that were highlighted in Section 4.3.8.2 of the EAG report. Therefore, the EAG still considers the uncertainty around utility values to be a Key Issue under a CUA, especially given that utilities at the PD state are a primary driver of the effectiveness results across both the untreated CLL and R/R CLL populations. The scenarios presented by the EAG explore the impact that uncertainty around the PD utility values have on cost-effectiveness results and, therefore, the EAG considers they are informative. The alternative utility scenarios provided by the Company were tested across the Company and EAG base-case models and, as presented in Table 2 and Table 3 above, the cost-effectiveness results did not change. Similarly, there was no noticeable change in the probability of zanubrutinib being a cost-effective in these analyses. The EAG also note that the utility value for PF from GID-TA10746 reported by the Company in Table 2 could not be found by the EAG from the source cited. The EAG maintains the position held in the EAG report that a CUA makes for a more accurate representation of the decision problem across both the untreated CLL and the R/R CLL populations, except for the comparison with ibrutinib in R/R CLL. Based on the EAG base-case and scenario analyses, zanubrutinib was the preferred treatment option due to the cost-savings associated with the drug. Incorporating uncertainty in the utility estimates still resulted in a [redacted] the probability that zanubrutinib would be considered cost-effective for the threshold values considered. [redacted] However, as previously mentioned, the EAG have concerns about the model structure adopted for the untreated CLL population which creates uncertainty in these results. In addition, the assumptions made by both the Company and the EAG to estimate cost-effectiveness in this population using

	a CUA are also subject to uncertainty which could affect conclusions (please see EAG response to Key Issues 4, 6 and 9 above and EAG response to Key Issue 8 below).

Issue 8: Immaturity of trial data and parametric survival functions in untreated CLL and R/R CLL	No	Whilst the Company acknowledges that data from the SEQUOIA and ALPINE trials are immature, the cost-effectiveness models make the best use of the data available. The issue of immature trial data is not new in the CLL landscape, as patients can live for a long time with current treatments. This issue has been evident across several previous CLL appraisals. In TA689, a similar median follow-up was reported for acalabrutinib monotherapy in ELEVATE-TN (28.4 months) as that reported in the zanubrutinib arm of SEQUOIA (16.35 months) in previously untreated CLL. Furthermore, a shorter follow-up was reported in the acalabrutinib arm of ASCEND (16.0 months) compared to the zanubrutinib arm of ALPINE (23.82 months) in R/R CLL. OS data from both ELEVATE-TN and ASCEND were immature, with median OS not reached in any treatment group. Similarly, immature OS data was evident in both the GLOW and CAPTIVATE trials reported in TA10746. The level of data immaturity reported in the zanubrutinib clinical trials is therefore aligned with that in previous appraisals.[4,25] The process of selecting a best-fitting distribution for extrapolation of survival data was aligned with the NICE DSU 14 guidelines.[30] Selection involved an assessment of clinical plausibility leveraging clinical expert opinion and comparing to published trial data, coupled with an assessment of statistical fit via measures such as Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). The Company explored the impact of alternative survival functions within their scenario analyses, and further scenario analyses were also conducted by the EAG. In all scenarios presented, zanubrutinib remained cost-effective.
EAG response:	The EAG acknowledges that data immaturity is not a new concern in submissions within the context of CLL and that this issue is not exclusive to this TA submission alone. Nevertheless, using the trial data available at the time of this submission, survival estimates presented wide confidence intervals which resulted in considerable uncertainty when assessing the efficacy of the intervention relative to its comparators under the MAIC models – it is the assumptions made by the Company on the basis of the results of these MAIC models that have been used by the Company to justify the CMA assumption of equivalent clinical effectiveness. As noted above the EAG note that the MAIC results cannot rule out that clinically important differences between treatments might exist.	

	The parametric survival models, probabilistic analyses, and sensitivity analyses presented by the Company in their submission, and by the EAG in the EAG report as scenario analyses, are informative to assess parameter uncertainty, but may not incorporate structural uncertainty or additional uncertainties caused by the lack of comparative head-to-head clinical evidence (e.g. differences in the trial design, data collection, or populations from the trials compared), the lack of data for certain subpopulations (e.g. the inability to assess relative effectiveness from data on untreated "high-risk" patients only), and the lack of longer-term survival (e.g. OS data from SEQUOIA in particular had a low event count and the MAIC results based on it had worse point estimates of OS from zanubrutinib with wide confidence intervals, despite PFS improvements) that could either reinforce of disprove the assumption of clinical effectiveness.[6]

Additional issues

No additional issues were identified.

Summary of changes to the company's cost-effectiveness estimate(s)

The Company has not submitted a revised base case.

Sensitivity analyses around revised base case

Not applicable.

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