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:

1. **Comments on the Draft Guidance from BeiGene**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Leukaemia Care
   b. UK CLL Forum-Royal College of Pathologists-British Society for Haematology
   c. Abbvie
   d. Janssen-Cilag

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank):	BeiGene UK 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 • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Submitting Company
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Summary of the Company's position** The Company would like to thank the Committee for the opportunity to respond to the Appraisal Consultation Document (ACD). The Company welcomes the Committee's acknowledgement that: - zanubrutinib is a tolerable and safe treatment for previously untreated chronic lymphocytic leukaemia (CLL) and relapsed or refractory (R/R) CLL. - zanubrutinib would be welcomed as a new treatment option. - the SEQUOIA trial is applicable to people regardless of suitability for fludarabine-cyclophosphamide-rituximab (FCR) or bendamustine-rituximab (BR). - the use of ALPINE data in R/R CLL is acceptable as a proxy for the previously untreated CLL population with a 17p deletion or TP53 mutation. However, the Company are concerned that despite the evidence submitted, coupled with the support from CLL patient group representatives and clinical experts, the Committee have not recommended zanubrutinib for the treatment of patients with: - previously untreated CLL with a 17p deletion or TP53 mutation. - previously untreated CLL without 17p deletion or TP53 mutation for whom FCR or BR is unsuitable. - R/R CLL. The Company maintain that zanubrutinib will be used as an alternative Bruton's tyrosine kinase inhibitor (BTKi) monotherapy in clinical practice and that fixed-duration therapies, i.e. venetoclax-based regimens, are not relevant comparators. This position is supported by consensus statements obtained from 11 UK clinical experts via a Delphi panel.[1] However, in response to the ACD and to alleviate any uncertainty, the Company would like to present the following data for consideration by the Committee: - cost-utility comparison versus acalabrutinib in patients with previously untreated CLL either with or without a 17p deletion and/or TP53 mutation for whom FCR or BR is unsuitable and in patients with R/R CLL. - cost-utility comparison versus ibrutinib in patients with previously untreated CLL either with a 17p deletion and/or TP53 mutation and in patients with R/R CLL.

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Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	- cost-utility comparisons versus ibrutinib-venetoclax (I-V) in patients (older patients with and/or comorbidities and younger patients without comorbidities) with previously untreated CLL. - cost-utility comparison versus venetoclax-obinutuzumab (VenO) in patients with previously untreated CLL either with or without a 17p deletion and/or TP53 mutation for whom FCR or BR is unsuitable. - cost-utility comparison versus venetoclax-rituximab (VenR) in patients with R/R CLL. Comments 2 to 7 present the Company's position on these points in further detail. The scenarios presented in Table 1 have been validated with UK clinical experts and are considered to be clinically plausible and suitable for decision-making. Additional scenario analyses have been conducted to alleviate any further uncertainty and are presented in Comments 4 to 7. In addition, the previously untreated cost-utility analyses are presented using the latest data set available from SEQUOIA (data cut-off [DCO]: 31 October 2022), which was presented at the European Haematology Association conference in June 2023 and summarised in Appendix 1.[2] Late-breaking data from ALPINE (DCO: 15 May 2023)[3] has been used to validate the survival extrapolations from ALPINE (DCO: 01 December 2021) which were previously included in the models. Given the short timeframe between the DCO and ACD response deadline, the economic models and ITCs have not been updated to utilise the latest ALPINE data. In addition, as the latest ALPINE data is consistent with the 2021 DCO that was utilised in the ITCs and economic models, this would have unlikely impacted the conclusions of the ITCs and the models. A summary of the latest clinical evidence from ALPINE is presented in Appendix 2. In the base case analysis, zanubrutinib is less costly and more effective than ibrutinib and acalabrutinib, and hence dominates acalabrutinib and ibrutinib in both the previously untreated and R/R CLL populations. In exploratory analyses, compared with fixed-duration therapies, zanubrutinib was the most cost-effective treatment option across all comparisons: • In previously untreated CLL, zanubrutinib is less costly and more effective than both VenO and I-V (across both older and younger patient groups), and hence dominates the fixed-duration therapies

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	• In R/R CLL, zanubrutinib is less costly and less effective than VenR, generating a Southwest (SW) quadrant incremental cost-effectiveness ratio (ICER) of £440,995 (the cost-effectiveness threshold is inverted in the SW quadrant). Across all scenario analyses performed (addressing uncertainties of survival assumptions, comparative efficacy, subsequent treatment and utility sources), zanubrutinib remains a cost-effective treatment option across all comparisons and populations. Mean probabilistic costs and quality-adjusted life years (QALYs) lie close to the deterministic results for the base-case setting and across all scenario analyses, demonstrating the robustness of the Company's analyses. Probabilistic scenario analyses (PSA) were conducted across all scenarios at 1,000 iterations, varying individual parameters within their confidence interval using a distribution appropriate to the parameter type. Specifically hazard ratios (HRs) from the matching-adjusted indirect comparisons (MAICs) were varied using their confidence intervals along a log-normal distribution, hence the PSA takes into account and addresses uncertainty related to the MAIC results. Further details of the cost-effectiveness comparisons are presented in Comments 4 to 7.

NICE National Institute for Health and Care Excellence

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

Table 1. Cost-effectiveness analyses for zanubrutinib versus comparators (deterministic)*

Scenario	Inc. cost (£)	Inc. QALYs	ICER (£)†
Previously untreated CLL			
1. Comparison with acalabrutinib (patients with or without a 17p deletion and/or TP53 mutation for whom FCR or BR is unsuitable)	[redacted]	[redacted]	Dominating
2. Comparison with ibrutinib (patients with a 17p deletion and/or TP53 mutation)	[redacted]	[redacted]	Dominating
3. Comparison with I-V (older patients and/or with comorbidities with previously untreated CLL)	[redacted]	[redacted]	Dominating
4. Comparison with I-V (younger patients without comorbidities with previously untreated CLL)	[redacted]	[redacted]	Dominating
5. Comparison with VenO (patients with or without a 17p deletion and/or TP53 mutation for whom FCR or BR is unsuitable)	[redacted]	[redacted]	Dominating
R/R CLL			
1. Comparison with acalabrutinib	[redacted]	[redacted]	Dominating
2. Comparison with ibrutinib	[redacted]	[redacted]	Dominating
3. Comparison with VenR	[redacted]	[redacted]	440,995 (SW)†

BR, bendamustine-rituximab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine-cyclophosphamide-rituximab; I-V, ibrutinib-venetoclax; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; R/R – relapsed/refractory; VenO, venetoclax-obinutuzumab; VenR, venetoclax-rituximab.*Results presented using zanubrutinib Patient Access Scheme (PAS). † An ICER in the SW is assessed via an inverted threshold, such that an ICER > £30,000 can be considered cost-effective.

2 **Positioning and comparators**

The Company maintain that zanubrutinib will be used as an alternative to currently approved BTKis in clinical practice and that fixed-duration therapies are not relevant comparators. This position is supported by consensus statements obtained from a Delphi panel conducted with 11 UK clinical experts:[1]

- *"A major decision point in CLL treatment is between fixed-duration therapies and continuous monotherapies, after which the options available within each treatment modality are considered."*
- *"The availability of zanubrutinib monotherapy in previously untreated and relapsed/refractory CLL would not impact any clinical decision to prescribe a fixed-duration treatment versus a continuous BTKi monotherapy."*
- *"Changing the mechanism of action after progression is standard practice for 2L treatment of CLL, therefore the majority of patients eligible for zanubrutinib in R/R*

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	would be those who had received a fixed-duration therapy in 1L, and the majority of patients eligible for VenR would be those who had received a BTKi treatment in the 1L." • *"VenR is not a relevant comparator to zanubrutinib in the R/R setting, given the majority of patients receiving VenR would be BTKi experienced, which does not align with the eligibility criteria of ALPINE or the anticipated use of zanubrutinib in UK clinical practice."* ***Previously untreated CLL*** As per the 2022 British Society for Haematology (BSH) guidelines, treatment choices are made jointly by clinicians and patients, based on disease-related characteristics, patient preference and toxicity profile.[4] Patient preference is a key component of the treatment decision with patients deciding whether oral continuous or more intensive fixed-duration therapies with harsher toxicities and more invasive administration and monitoring requirements are better suited to their lifestyle. Clinical consensus gained from a Delphi panel confirmed that zanubrutinib, as a next-generation BTKi, will not alter the treatment paradigm in CLL or have an impact on the treatment decision of whether to initiate with a continuous or fixed-duration therapy.[1] As such, the introduction of zanubrutinib will only impact the decision as to which continuous therapy patients will receive. Consequently, it is only appropriate to compare zanubrutinib to other continuous therapies such as acalabrutinib and ibrutinib monotherapy, and fixed-duration therapies, such as VenO and I-V, would not be considered comparators in clinical practice. Furthermore, the clinical experts agreed via a consensus at the Delphi panel that I-V does not reflect current established NHS clinical practice for all previously untreated patients with CLL.[1] ***Relapsed/refractory CLL*** As per the 2022 BSH guidelines, a 'sequencing' approach is recommended when selecting the optimal strategy for patients who have relapsed following treatment with front-line targeted agents.[4] Treatment sequencing suggests that the optimal treatment following progression is driven by choice of front-line therapy: • For patients progressing following front-line treatment with a BTKi therapy, a fixed-duration therapy, namely VenR, is recommended. • For patients progressing following front-line treatment with a fixed-duration therapy, such as VenO, a BTKi therapy is recommended.

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	Clinical experts agreed via consensus in a Delphi panel that a change in mechanism of action after progression from first-line to second-line is the standard practice for second-line treatment for CLL, highlighting this is an overarching principle of cancer therapy.[1] As such, VenR is not considered an appropriate comparator within the appraisal of zanubrutinib for the following reasons: • Whilst a minority of patients may receive venetoclax retreatment with VenR after progression with VenO, this decision is due to patient preference if a patient has had a positive experience with venetoclax or in circumstances where a BTKi is not suitable. As such, these instances will not be impacted by the introduction of zanubrutinib into the treatment pathway. Furthermore, evidence for retreatment with venetoclax is limited as highlighted in the 2022 BSH guidelines and UK clinical expert opinion.[4] • I-V was only recently approved by NICE, and there is currently limited data on the treatment sequencing algorithm following progression on I-V. However, I-V is a venetoclax-based fixed-duration therapy and as such it is hypothesised that patients would receive continuous BTKi monotherapy following progression to provide a change in the mechanism of action. The use of BTKi therapy following progression on I-V is supported by the CAPTIVATE and GLOW trials, which mandate that patients should receive BTKi monotherapy following disease progression. This was further supported by UK clinical experts who agreed in consensus that "*Based on the current evidence from GLOW/CAPTIVATE (continuous BTKi after progression), the most likely subsequent treatment after ibrutinib plus venetoclax is continuous BTKi monotherapy*".[1] • Chemoimmunotherapy (CIT) usage has dramatically declined following the introduction of newer, more efficacious targeted therapies with increasingly limited number of patients progressing to 2L following CIT, and therefore, this is no longer a consideration in clinical practice.
3	**Appropriateness of existing economic model for decision making** The Company maintains that the economic models used to assess the cost-effectiveness of zanubrutinib in patients with previously untreated CLL and in patients with R/R CLL are fit for purpose and suitable for decision making. Although the Company's base case adopted cost-minimisation analyses in both the previously untreated and R/R CLL populations, the Excel models were both developed for

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	the purpose of a cost-utility analysis. Therefore, the Excel models include all appropriate functionality to conduct cost-utility analyses. The cost-minimisation base case was adopted in the model by assuming equivalent efficacy across BTKi treatments within the cost-utility framework. In the previously untreated CLL model, equivalent efficacy was assumed by setting the time-to-progression (TTP) HR of ibrutinib and acalabrutinib compared to zanubrutinib to equal one. The model was not altered any further compared to the cost-utility analysis and no functional or structural changes were made. Similarly, in the R/R CLL model, equivalent efficacy was assumed by setting the progression-free survival (PFS) and overall survival (OS) HRs of ibrutinib and acalabrutinib compared to zanubrutinib to equal one rather than by limiting the functionality of the model compared to a cost-utility analysis. Therefore, the Company's decision to set the base cases to a cost-minimisation analyses did not introduce any structural uncertainties that impacted the cost-utility analyses, and the models should not be considered a limiting factor in decision making. ***Constant relative hazards*** The Company also maintains that the assumption of constant relative hazards over time is appropriate. In previously untreated CLL, the MAIC conducted for zanubrutinib versus acalabrutinib using ELEVATE-TN found no evidence that the proportional hazards (PH) assumption was violated (Document B, Section B.2.9.1.3). In R/R CLL, the MAICs conducted for zanubrutinib versus acalabrutinib using ELEVATE-RR and ASCEND both found no evidence that the PH assumption was violated (Document B, Section B.2.9.2.3 and Document B, Section B.2.9.3.3). In addition, it is clinically reasonable to assume a proportional treatment effect given that zanubrutinib, acalabrutinib and ibrutinib are all BTKis and share the same mechanism of action. Furthermore, the application of a constant HR to generate survival estimates for comparator treatments is a commonly adopted method in oncology, and specifically in recent and relevant CLL appraisals (NICE TA663, NICE TA891).[5,6] ***Safety modelling*** Both economic models assume that adverse events (AEs) occur in the first four weeks of treatment (the first model cycle) as a simplifying assumption. However, the models consider the duration of AEs when calculating the impact on costs and quality of life. To assess the impact of AEs on quality of life, a disutility is applied in the model for the duration of the AE to determine the average QALY loss due to each AE episode. In addition, the unit cost applied for each AE is based on the average length of the AE as collected by the NHS Reference Cost Tariff.

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	Assessing AEs within the first model cycle only is standard practice in economic modelling and the same method has been used in other recent and relevant NICE appraisals for treatments in CLL, including TA891 and TA689.[6,7] The EAG highlighted that some AEs, such as cataracts or hypertension, would take longer than four weeks to resolve. In both TA891 and TA689, hypertension was included as an AE in the economic models and in TA891 cataracts was included. In each case, the impact of the AEs on costs and quality of life were only considered within the first model cycle.[6,7] Based on the above, the Company maintains that applying the cost and disutility associated with AEs to the first cycle is an appropriate method for decision making given that the costs and utility both take the duration of the AE into account. Furthermore, zanubrutinib might offer safety and tolerability advantages over existing BTKis through reduced inhibition of off-target kinases which reduces the risk of cardiac AEs.[8] As such, more detailed modelling of safety will likely lead to a benefit in favour of zanubrutinib which therefore suggest that the current modelling estimates can be considered conservative. Nonetheless, to help alleviate concerns expressed by the Committee, additional cardiac AEs have been added to the model. In addition, the Company acknowledge that the reoccurring AEs are not explicitly modelled, though this is a common simplification made in economic modelling often driven by a lack of sufficient data for all relevant treatments, which could underestimate the costs and quality of life impact of AEs. However, as zanubrutinib offers safety and tolerability advantages over existing BTKis, this can be considered conservative as modelling of AE reoccurrence will likely lead to a benefit in favour of zanubrutinib. ***Duration of treatment effect*** Both economic models assume that the treatment effect of BTKis is maintained whilst patients are in the progression-free (PF) health state. In line with the respective SmPCs, patients are modelled to receive BTKi treatment to progression and as such, the models apply the costs and treatment effect of BTKis until patients progress to the progressed disease (PD) health state. Beyond this point when patients are in the PD health state, it is assumed that all patients go on to receive other targeted therapies. In the previously untreated CLL model, the efficacy of subsequent treatments is explicitly modelled within the PPS and PFS 2L modelling based on efficacy data for the subsequent treatment. In the R/R CLL, the model does not assume that the treatment benefit continues, rather that the benefit in the PD state comes from the subsequent lines of treatment received, as per standard assumptions for a partitioned survival model, as this is inherently captured in the OS trial endpoint.

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	All data informing the models has been validated using long-term data for BTKis and UK clinical expert opinion. Long-term results from RESONATE-2 show sustained PFS and OS benefits for previously untreated patients receiving first-line ibrutinib compared to those receiving chlorambucil after eight years of follow-up data.[9] In the R/R CLL setting, the ASCEND study showed that median OS has not been reached despite more than four years of follow-up data and acalabrutinib maintains favourable efficacy versus BR.[10] In addition, both NICE TA429 and TA689 assume that patients are treated with a BTKi until progression without a loss of treatment effect.[7,11] The Company, therefore, maintains that the modelling assumptions for long-term survival is appropriate for decision making purposes based on real-world evidence, past precedence and UK clinical expert opinion.
4	**Revised cost-effectiveness results for comparisons with alternative BTKis – previously untreated CLL** In light of the discussion during the first ACM and feedback from the Committee presented in the ACD, the Company have revised their base case comparison versus alternative BTKis (acalabrutinib and ibrutinib) in patients with previously untreated CLL. A summary of the revised base case settings is presented in Table 2. To alleviate concerns expressed by the Committee on the immaturity of the data, clinical outcomes from an updated data cut of SEQUOIA (DCO: 31 October 2022, results presented in Appendix 1) were used to update the survival and MAIC analyses used to inform the economic model. The updated survival analyses are presented in Appendix 7 and results from the updated MAIC versus ELEVATE-TN are presented in Appendix 3. To further alleviate concerns expressed by the Committee, additional cardiac AEs have been added to the model and the impact of alternative utility values has been explored within scenario analyses. Revised base case results using updated clinical data and additional AEs are presented in Table 3, with key scenario analyses presented in Table 4. Of note, a scenario has been included using COVID-19 adjusted MAIC outputs. This scenario adjusts for the impact of COVID-19 observed in the SEQUOIA trial that was not a factor in the ELEVATE-TN trial. For further details, please see Appendix 3. In the base-case analysis, zanubrutinib is less costly and more effective than ibrutinib and acalabrutinib, and hence dominates both BTKi treatment alternatives. Across all scenario analyses performed (addressing the uncertainty of survival assumptions, comparative effectiveness and utility sources), zanubrutinib remains the preferred BTKi treatment option for patients with previously untreated CLL. Mean probabilistic results lie close to the deterministic results for the respective base cases and across all scenario analyses, demonstrating the robustness of

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

the Company's analyses, with a [redacted]% probability of being cost-effective at a WTP threshold of £30,000 per QALY gained.

Table 2: Summary of Company base case for comparisons with alternative BTKis – previously untreated CLL

Setting	Updated Company base case	Notes
Modelling methodology	Cost-utility analysis using 3-state semi-Markov model structure (PF, PD and death) over a lifetime horizon.	As per request from the EAG and Committee, the analyses were updated using a cost-utility approach.
Comparators	Acalabrutinib: Patients with or without a 17p deletion and/or TP53 mutation for whom FCR or BR is unsuitable. Ibrutinib: Patients with a 17p deletion and/or TP53 mutation.	BTKi comparisons as previously submitted and accepted by the Committee.
Comparative efficacy	Acalabrutinib: MAIC (Model 1) using pooled SEQUOIA Arm A+C (DCO: 31 October 2022) and ELEVATE-TN. Ibrutinib: Direct H2H from 'high-risk' subgroup of patients in ALPINE (DCO: 15 May 2023)[3]	ITC approach as previously submitted and accepted by the Committee. Acalabrutinib: MAIC updated using latest SEQUOIA data cut, with Model 1 used to inform the base case given that the model adjusted for the most covariates whilst maintaining sufficient sample size. This was validated with UK clinical experts in 1:1 interviews. Ibrutinib: Using high risk R/R data as a proxy for previously untreated high risk CLL was accepted by the Committee. However, the HR has been updated from latest ALPINE data cut used (DCO: 15 May 2023).[3]
TTP modelling	Zanubrutinib: Direct extrapolation of pooled SEQUOIA Arm A+C (DCO: 31 October 2022) using the Weibull distribution. Alternative BTKis: PFS HRs (ELEVATE-TN MAIC Model 1 and ALPINE H2H data) applied to extrapolated zanubrutinib curve.	Following a further data cut, the survival analyses were updated to use the most up to date available data from SEQUOIA. The Weibull distribution for TTP and PrePS best aligns with the data available from RESONATE-2 after 8 years of follow-up for PFS. The use of the Weibull curve was validated with clinical experts.
PrePS modelling	Zanubrutinib: Direct extrapolation of pooled SEQUOIA Arm A+C (DCO: 31	The Weibull distribution for TTP and PrePS best aligns with the data available

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

			October 2022) using the Weibull distribution. Alternative BTKis: PFS HRs (ELEVATE-TN MAIC Model 1 and ALPINE H2H data) applied to extrapolated zanubrutinib curve.	from RESONATE-2 after 8 years of follow-up for PFS. The methodology suggested by the EAG was adopted in the Company base case with one amendment for the comparators. The EAG suggested that the OS HR be applied to the extrapolated SEQUOIA data. However, the Company firmly believe that the PFS HR would be more appropriate to use. 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. 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.
		Subsequent treatment modelling	100% patients receive VenR following progression on BTKi monotherapy, modelled using MURANO. PPS extrapolation: Exponential distribution. PFS 2L extrapolation: Gompertz distribution.	Reflects subsequent treatment pathway in clinical practice, as validated by UK clinical experts. Subsequent treatment pathway aligned with PPS data source; extrapolations as previously submitted and accepted by the Committee and adopted by the EAG in their base case analysis.
		Drug acquisition costs	BNF treatment list prices, with PAS for zanubrutinib.	As per original Company submission, aligned with EAG base case analysis.
		Treatment duration	Until progression (or death).	As per original Company submission, based on the licensed indications for BTKis, and aligned with EAG base case analysis.
		Resource use	Resource values from the literature (NICE TA689).[12]	As per original Company submission, aligned with EAG base case analysis.
		End of life	Resource use and costs (Round 2015).[13]	As per original Company submission, aligned with EAG base case analysis.

Please return to: **NICE DOCS**

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

TLS management	One time monitoring for venetoclax (Seymour 2018 and NICE TA561).[14,15]	As per original Company submission, aligned with EAG base case analysis.
Utility values	PF: EQ-5D score for the age and sex-matched general population.[7] PD: Holzner et al (2004).[16]	Utility values as adopted in EAG base case and aligned with method adopted by the EAG in NICE TA689.
Safety modelling	AE rates from SEQUOIA, ELEVATE-TN and RESONATE-2. Additional cardiac AEs included (AF and cardiac failure).	Following discussion in Committee meeting, additional cardiac AEs have been added to the model. AEs updated to use the most up to date available data from SEQUOIA.

AE, adverse event; AF, atrial fibrillation; BNF, British National Formulary; BR, bendamustine-rituximab; BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; CUA , cost-utility analysis; DCO, data cut-off; EAG, Evidence Assessment Group; FCR, fludarabine-cyclophosphamide-rituximab; H2H, head-to-head; HR, hazard ratio; ITC – indirect treatment comparison; NICE, National Institute for Health and Care Excellence; MAIC, matching-adjusted indirect comparison; PAS, patient access scheme; PD, progressed; PF, progression-free; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; OS overall survival; TP53, tumour protein 53; TTP, time-to-progression; 2L, second-line; VenR, venetoclax-rituximab.

Table 3: Revised Company base case analyses versus alternative BTKis – previously untreated CLL

	Total costs (£)	Total QALYs	Incremental cost vs. zanubrutinib (£)	Incremental QALY vs. zanubrutinib	ICER (£/QALY) vs. zanubrutinib
Deterministic					
Zanubrutinib	[redacted]	[redacted]	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	1.116	Dominating
Acalabrutinib	[redacted]	[redacted]	[redacted]	0.115	Dominating
Probabilistic (n=1,000 iterations)					
Zanubrutinib	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	[redacted]	1.096	Dominating
Acalabrutinib	[redacted]	[redacted]	[redacted]	0.098	Dominating

BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 4: Key scenario analyses versus alternative BTKis – previously untreated CLL

Scenario	ICER (£/QALY) vs. acalabrutinib		ICER (£/QALY) vs. ibrutinib	
	Deterministic	Probabilistic	Deterministic	Probabilistic
Base Case	Dominating	Dominating	Dominating	Dominating
TTP endpoint (2021 IRC)	Dominating	Dominating	Dominating	Dominating

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

TTP/PrePS curve for zanubrutinib (Log-logistic)	Dominating	Dominating	Dominating	Dominating
TTP/PrePS curve for zanubrutinib (exponential)	Dominating	Dominating	Dominating	Dominating
PPS curve for BTKi (Weibull)	Dominating	Dominating	Dominating	Dominating
2L PFS curve for BTKi (Generalised Gamma)	Dominating	Dominating	Dominating	Dominating
Pooled (cost-utility - ELEVATE-TN MAIC Model 2)	Dominating	Dominating	N/A	N/A
Pooled (cost-utility - ELEVATE-TN MAIC Model 1 COVID adjustment)	Dominating	Dominating	N/A	N/A
Pooled (cost-utility - ELEVATE-TN MAIC Model 2 COVID adjustment)	Dominating	Dominating	N/A	N/A
Arm A (cost-utility - ELEVATE-TN MAIC Model 1 and H2H ALPINE data)	Dominating	Dominating	Dominating	Dominating
Arm C (cost-utility - ELEVATE-TN MAIC Model 1 and H2H ALPINE data)	Dominating	Dominating	Dominating	Dominating
SEQUOIA trial-based utilities	Dominating	Dominating	Dominating	Dominating
TA689 utilities (PF = 0.78; PD = 0.60)	Dominating	Dominating	Dominating	Dominating
TA663 utilities (PF = 0.67; PD = 0.60)	Dominating	Dominating	Dominating	Dominating
GID-TA10756 utilities (PF = 0.67; PD = 0.60)	Dominating	Dominating	Dominating	Dominating

AE, adverse events; BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; COVID, coronavirus disease; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; R/R, relapsed/refractory; PFS, progression-free survival; PrePS, pre-progression survival; TTP – time-to-progression; QALY, quality-adjusted life year; 2L, second-line

5	**Cost-utility analysis versus fixed-duration therapies – previously untreated CLL** As outlined in Comment 2, the Company maintain that comparisons with fixed-duration therapies, namely VenO and I-V, are not relevant to this NICE appraisal given that

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	zanubrutinib is positioned as an alternative BTKi treatment and the introduction of zanubrutinib will not impact the clinical decision of whether to prescribe a fixed-duration or continuous treatment. Nevertheless, to alleviate concerns presented by the Committee in the ACD, the Company have conducted exploratory cost-effectiveness analyses versus VenO and I-V in patients with previously untreated CLL. Details of the MAIC comparing zanubrutinib with VenO in CLL14 are presented in Appendix 4. Details of the MAIC comparing zanubrutinib with I-V in GLOW are presented in Appendix 5 and details of the MAIC comparing zanubrutinib with I-V in CAPTIVATE are presented in Appendix 6. Analyses using ASCEND were conducted to inform PPS and PFS 2L modelling following progression on fixed-duration therapy, as presented in Appendix 8. The Company's existing economic model for patients with previously untreated CLL was adapted to include VenO and I-V as comparators. The model settings, data sources and assumptions presented in Table 2 are also applicable to this comparison. A summary of settings specific to VenO and I-V are presented in Table 5. For the comparison with I-V, two base cases are presented to inform the efficacy of zanubrutinib versus I-V – one using the GLOW trial and one using the CAPTIVATE trial. As the CAPTIVATE trial included younger and fitter (without comorbidities) patients, the MAIC using CAPTIVATE was used to provide an estimate of comparative efficacy with zanubrutinib in younger and fitter patients. In contrast, the GLOW trial included older or less fit (with comorbidities) patients so the MAIC using GLOW was more appropriate to inform a comparison in this population of patients. Given the lack of crossover between the populations in the CAPTIVATE and SEQUOIA trials (specifically the CAPTIVATE trial was a much younger population than SEQUOIA), the ESS of the analyses after matching between these trials was lower than that observed in the other MAICs conducted (versus VenO and acalabrutinib) for the zanubrutinib arm. However, the Company consider a comparison between CAPTIVATE and SEQUOIA to be suitable for decision making given both the EAG and the Committee deemed the SEQUOIA population to be representative of all previously untreated patients with CLL, regardless of fitness status. To preserve ESS the matching variables were limited to key prognostic factors for the base-case analysis, with further variables explored in a scenario analyses. All new MAICs conducted in response to the ACD were validated with UK clinical experts in 1:1 interviews. Exploratory base-case results are presented in Table 6 and Table 7, with key scenario analyses presented in Table 8 and Table 9. In the base-case analysis zanubrutinib is less

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

costly and more effective than both VenO and I-V (across both older and younger groups), and hence dominates the fixed-duration therapies. Across all scenario analyses performed (addressing the uncertainty of survival assumptions, comparative effectiveness and utility sources), zanubrutinib remains a cost-effective and efficacious treatment option for patients with previously untreated CLL. The scenario considering the COVID-19 adjustment in the MAICs was only applied in the VenO comparison given that GLOW and CAPTIVATE trials were conducted during the pandemic. Mean probabilistic results lie close to the deterministic results for the respective base cases and across all scenario analyses, demonstrating the robustness of the Company's analyses.

Table 5: Summary of model settings for comparisons with fixed-duration therapies – previously untreated CLL

Setting	Updated Company base case	Notes
Comparators	VenO: Patients with or without a 17p deletion and/or TP53 mutation for whom FCR or BR is unsuitable. I-V: Patients with or without a 17p deletion and/or TP53 mutation.	As per respective NICE recommendations.
Comparative efficacy	VenO: MAIC using pooled SEQUOIA Arm A+C (DCO: 31 October 2022) and CLL14. I-V: MAIC using pooled SEQUOIA Arm A+C (DCO: 31 October 2022) and GLOW (Model 1) in older patients and/or patients with comorbidities. An additional model (MAIC Model 2) was considered as a scenario. I-V: MAIC using pooled SEQUOIA Arm A+C (DCO: 31 October 2022) and CAPTIVATE (Model 2) in younger patients without comorbidities. Baseline age in the model is set to the median age after matching from the adjusted SEQUOIA data set (60 years) to reflect the younger age of this patient population.	VenO: New MAIC conducted using CLL14. The matching model was validated by UK clinical experts to ensure that the model captured key prognostic factors and treatment effect modifiers. I-V: Two new MAICs conducted using CAPTIVATE (Model 2) and GLOW (Model 1). Matching models for GLOW and CAPTIVATE were validated by UK clinical experts. Both experts agreed that Model 2 for CAPTIVATE (which captures key prognostic factors) was the most appropriate for the base-case analysis. Model 1 which captures both treatment effect modifiers and prognostic factors was considered in a scenario analyses. Furthermore, both experts agreed that GLOW Model 1 was the most appropriate for the base-case analysis, with a scenario analysis considering a second model (MAIC Model 2)

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	TTP modelling	VenO: PFS HR (CLL14 MAIC) applied to extrapolated zanubrutinib curve. I-V: PFS HR (GLOW/CAPTIVATE MAIC) applied to extrapolated zanubrutinib curve.	Methodology in line with comparisons with alternative BTKis. The proportional hazards assumption cannot be rejected for zanubrutinib versus either I-V (GLOW only) or VenO.
	PrePS modelling	VenO: PFS HR (CLL14 MAIC) applied to extrapolated zanubrutinib curve. I-V: PFS HR (GLOW/CAPTIVATE MAIC) applied to extrapolated zanubrutinib curve.	Methodology in line with comparisons with alternative BTKis. The proportional hazards assumption cannot be rejected for zanubrutinib versus either I-V (GLOW only) or VenO.
	Subsequent treatment modelling	100% patients receive acalabrutinib following progression on fixed-duration therapy, modelled using ASCEND PPS. A scenario analysis was modelled in which a proportion of patients received VenR after treatment with I-V/VenO. PPS extrapolation: Exponential distribution. PFS 2L extrapolation: Exponential distribution.	Reflects subsequent treatment pathway in clinical practice, as validated by UK clinical experts. Subsequent treatment pathway aligned with PPS data source. PPS extrapolation: Exponential distribution selected as the extrapolation has the lowest AIC and aligns with the accepted base case in NICE TA689 and the assumption of no increasing risk post-progression as applied for the BTKi treatments. PFS 2L extrapolation: Exponential distribution selected as the curve presents the only estimation without a flattening or plateauing tail.
	Safety modelling	AE rates from CLL14 and GLOW/CAPTIVATE, applied as a one-off in the first cycle.	Methodology in line with comparisons with alternative BTKis. Please note, only Grade 3/4 occurring in ≥5% of patients were reported for I-V in the relevant literature.[17,18] As the model assesses Grade 3/4 occurring in ≥2% of patients treated with BTKis, the costs and quality of life decrement related to AEs will be underestimated for I-V and will likely be higher than modelled.

AE, adverse events; AIC, Akaike's information criterion; BR, bendamustine-rituximab; BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; DCO, data cut-off; FCR, fludarabine-cyclophosphamide-rituximab; HR – hazard ratio; I-V, ibrutinib-venetoclax; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; R/R, relapsed/refractory; PFS, progression-free survival; PPS, post-progression survival; TTP – time-to-progression; QALY, quality-adjusted life year; VenO, venetoclax-obinutuzumab; 2L, second-line.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

Table 6: Exploratory Company analyses with fixed-duration therapies – previously untreated CLL (older population and/or comorbidities)

	Total costs	Total QALYs	Incremental cost vs. zanubrutinib	Incremental QALY vs. zanubrutinib	ICER (£/QALY) vs. zanubrutinib
Deterministic					
Zanubrutinib	[redacted]	[redacted]	-	-	-
VenO (CLL14)	[redacted]	[redacted]	[redacted]	0.493	Dominating
I-V (GLOW)	[redacted]	[redacted]	[redacted]	0.490	Dominating
Probabilistic					
Zanubrutinib	[redacted]	[redacted]		-	-
VenO (CLL14)	[redacted]	[redacted]	[redacted]	0.395	Dominating
I-V (GLOW)	[redacted]	[redacted]	[redacted]	0.417	Dominating

CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; I-V, ibrutinib-venetoclax; QALY, quality-adjusted life year; VenO, venetoclax-obinutuzumab

Table 7: Exploratory Company analyses with I-V fixed-duration therapy – previously untreated CLL (younger population without comorbidities)

	Total costs	Total QALYs	Incremental cost vs. zanubrutinib	Incremental QALY vs. zanubrutinib	ICER (£/QALY) vs. zanubrutinib
Deterministic					
Zanubrutinib	[redacted]	[redacted]	-	-	-
I-V (CAPTIVATE)	[redacted]	[redacted]	[redacted]	1.726	Dominating
Probabilistic					
Zanubrutinib	[redacted]	[redacted]			
I-V (CAPTIVATE)	[redacted]	[redacted]	[redacted]	1.355	Dominating

CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; I-V, ibrutinib-venetoclax; QALY, quality-adjusted life year

Table 8: Key scenario analyses with fixed-duration therapies – previously untreated CLL (older population and/or comorbidities)

Scenario	ICER (£/QALY)			
	VenO (CLL14)		I-V (GLOW)	
	Deterministic	Probabilistic	Deterministic	Probabilistic
Base Case	Dominating	Dominating	Dominating	Dominating
TTP endpoint (2021 IRC)	Dominating	Dominating	Dominating	Dominating
TTP/PrePS curve for zanubrutinib (Log-logistic)	Dominating	Dominating	Dominating	Dominating
TTP/PrePS curve for zanubrutinib (exponential)	Dominating	Dominating	Dominating	Dominating

Please return to: **NICE DOCS**

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

PPS curve for zanubrutinib (Weibull)	Dominating	Dominating	Dominating	Dominating
2L PFS curve for zanubrutinib (Generalised Gamma)	Dominating	Dominating	Dominating	Dominating
PPS curve for fixed-duration therapies (log-logistic)	Dominating	Dominating	Dominating	Dominating
2L PFS curve for fixed-duration therapies (log-logistic)	Dominating	Dominating	Dominating	Dominating
80%:20% BTKi:VenR after progression on first-line fixed-duration treatment (I-V/VenO)	Dominating	Dominating	Dominating	Dominating
Pooled (cost-utility – CLL14 MAIC COVID adjustment)	Dominating	Dominating	N/A	N/A
Pooled (cost-utility – GLOW MAIC 2)	N/A	N/A	Dominating	Dominating
Arm A (cost-utility)	Dominating	Dominating	Dominating	Dominating
Arm C (cost-utility)	Dominating	Dominating	Dominating	Dominating
SEQUOIA trial-based utilities	Dominating	Dominating	Dominating	Dominating
TA689 utilities (PF = 0.78; PD = 0.60)	Dominating	Dominating	Dominating	Dominating
TA663 utilities (PF = 0.67; PD = 0.60)	Dominating	Dominating	Dominating	Dominating
GID-TA10756 utilities (PF = 0.67; PD = 0.60)	Dominating	Dominating	Dominating	Dominating

AE, adverse events; CLL, chronic lymphocytic leukaemia; COVID, coronavirus disease; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; I-V, ibrutinib-venetoclax; MAIC, matching-adjusted indirect comparison; PD – progressed disease; PF – progression-free; PFS, progression-free survival; PrePS, pre-progression survival; TTP, time-to-progression; QALY, quality-adjusted life year; VenO, venetoclax-obinutuzumab; 2L, second-line.

Table 9: Key scenario analyses with I-V fixed-duration therapy – previously untreated CLL (younger population without comorbidities)

Scenario	ICER (£/QALY)	
	I-V (CAPTIVATE)	
	Deterministic	Probabilistic
Base Case	Dominating	Dominating
TTP endpoint (2021 IRC)	Dominating	Dominating
TTP/PrePS curve for zanubrutinib (Log-logistic)	Dominating	Dominating
TTP/PrePS curve for zanubrutinib (exponential)	Dominating	Dominating
PPS curve for zanubrutinib (Weibull)	Dominating	Dominating
2L PFS curve for zanubrutinib (Generalised Gamma)	Dominating	Dominating
PPS curve for fixed-duration therapies (log-logistic)	Dominating	Dominating
2L PFS curve for fixed-duration therapies (log-logistic)	Dominating	Dominating
80%:20% BTKi:VenR after progression on first-line fixed-duration treatment (I-V)	Dominating	Dominating
Arm A (cost-utility), with median age of 60 years	Dominating	Dominating
Arm C (cost-utility), with median age of 60 years	Dominating	Dominating
SEQUOIA trial-based utilities	Dominating	Dominating
TA689 utilities (PF = 0.78; PD = 0.60)	Dominating	Dominating
TA663 utilities (PF = 0.67; PD = 0.60)	Dominating	Dominating
GID-TA10756 utilities (PF = 0.67; PD = 0.60)	Dominating	Dominating

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	AE, adverse events; CLL, chronic lymphocytic leukaemia; COVID, coronavirus disease; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; I-V, ibrutinib-venetoclax; MAIC, matching-adjusted indirect comparison; PD, progress disease; PF, progression-free; PFS, progression-free survival; PrePS, pre-progression survival; TTP, time-to-progression; QALY, quality-adjusted life year; 2L, second-line.
6	**Revised cost-effectiveness results for comparisons with alternative BTKis – R/R CLL** In light of the discussion during the first ACM and the feedback from the Committee presented in the ACD, the Company have revised their base case comparison versus alternative BTKis (acalabrutinib and ibrutinib) in patients with R/R CLL. A summary of the revised base case settings is presented in Table 10. To further alleviate concerns expressed by the Committee, additional cardiac AEs have been added to the model and the impact of alternative utility values has been explored within scenario analyses. Furthermore, the survival extrapolations from ALPINE were validated using late-breaking data from ALPINE (DCO: 15 May 2023).[3] In the 15 May 2023 data cut, the 36-month event-free rate for patients in the zanubrutinib arm was reported as [redacted]%. This closely matched the model extrapolations which estimated the 36-month event-free rate for patients treated with zanubrutinib at [redacted]%. Revised base case results are presented in Table 11, with key scenario analyses presented in Table 12. In the base case analysis, zanubrutinib is less costly and more effective than ibrutinib and acalabrutinib, and hence dominates both BTKi treatment alternatives. Across all scenario analyses performed (addressing the uncertainty of survival assumptions, comparative effectiveness and utility sources), zanubrutinib remains the preferred BTKi treatment option for patients with R/R CLL. Mean probabilistic results lie close to the deterministic results for the respective base cases and across all scenario analyses, demonstrating the robustness of the Company's analyses, with a [redacted]% probability of being cost-effective at a WTP threshold of £30,000 per QALY gained. **Table 10: Summary of Company base case for comparisons with alternative BTKis – R/R CLL**

Setting	Updated Company base case	Notes
Modelling methodology	Cost-utility analysis using 3-state partitioned survival model structure (PF, PD and death) over a lifetime horizon.	As per request from the EAG and Committee, the analyses were updated using a cost-utility approach.
Comparators	Acalabrutinib: Patients with R/R CLL Ibrutinib: Patients with R/R CLL	BTKi comparisons as previously submitted and accepted by the Committee.

NICE National Institute for Health and Care Excellence

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	Comparative efficacy	Acalabrutinib: MAIC (Model 2) using ALPINE (DCO: 01 December 2021) and ELEVATE-RR. Ibrutinib: Direct H2H from ALPINE (DCO: 01 December 2021) using standard extrapolated survival curves.	ITC approach as previously submitted and accepted by the Committee. Acalabrutinib: ELEVATE-RR Model 2 selected to reduce uncertainty given that the ELEVATE-RR MAIC is anchored, whereas the ASCEND MAIC is unanchored. Model 2 selected over Model 1 as ESS is larger. Scenarios explored with ASCEND models. Ibrutinib: H2H evidence from ALPINE used; validated with late-breaking ALPINE data (DCO: 15 May 2023).[3]
	PFS modelling	Zanubrutinib: Direct extrapolation of ALPINE data (DCO: 01 December 2021) using the Weibull distribution (independent). Acalabrutinib: PFS HR (ELEVATE-RR MAIC Model 2) applied to extrapolated zanubrutinib curve. Ibrutinib: Direct extrapolation of ALPINE data (DCO: 01 December 2021) using the Weibull distribution (independent).	Use of independent Weibull distributions for zanubrutinib and ibrutinib is aligned with the original Company curve selection, as validated by UK clinical experts. The choice of model and distribution also aligns with the EAG base case curve selection. Application of PFS HR from MAIC for acalabrutinib is aligned with the EAG base case methodology.
	OS modelling	Zanubrutinib: Direct extrapolation of ALPINE data (DCO: 01 December 2021) using the joint Weibull distribution. Acalabrutinib: OS HR (ELEVATE-RR MAIC Model 2) applied to extrapolated zanubrutinib curve. Ibrutinib: Direct extrapolation of ALPINE data (DCO: 01 December 2021) using the joint Weibull distribution.	Weibull distribution is aligned with the original Company curve selection, as validated by UK clinical experts. The choice of distribution also aligns with the EAG base case curve selection for zanubrutinib and ibrutinib. Joint model adopted over independent models due to crossing of ibrutinib and zanubrutinib OS curves, which was deemed clinically unrealistic given the statistically significant benefit of zanubrutinib versus ibrutinib for PFS and the numerical trend in favour of zanubrutinib for OS. There is also no evidence to support a violation of the PH assumption. Application of OS HR from MAIC for acalabrutinib is aligned with the EAG base case methodology.

Please return to: **NICE DOCS**

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	Subsequent treatment modelling	80% VenR, 20% idelalisib-rituximab after first-line BTKi treatment.	Reflects subsequent treatment pathway in clinical practice, as validated by UK clinical experts. Accepted by the Committee and adopted by the EAG in their base case analysis.
	Drug acquisition	BNF treatment list prices, with PAS for zanubrutinib.	As per original Company submission, aligned with EAG base case analysis.
	Treatment duration	Until progression (or death).	As per original Company submission, based on the licensed indications for BTKis, and aligned with EAG base case analysis.
	Resource use	Resource values from the literature (NICE TA689).[12]	As per original Company submission, aligned with EAG base case analysis.
	End of life	Resource use and costs (Round 2015).[13]	As per original Company submission, aligned with EAG base case analysis.
	TLS management	One time monitoring for venetoclax (Seymour 2018 and NICE TA561).[14,15]	As per original Company submission, aligned with EAG base case analysis.
	Utility values	PF: 0.748 (NICE TA561).[14] PD: 0.60 Holzner et al (2004).[16]	Consistent with Company's original base case, utility values as adopted in EAG base case.
	Safety modelling	AE rates from ALPINE and ASCEND. Additional cardiac AEs included (AF and cardiac failure).	Following discussion in Committee meeting, additional cardiac AEs have been added to the model.

AE, adverse events; AF, atrial fibrillation; BTKi, Burton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; DCO, data cut-off; EAG, Evidence Assessment Group; ESS, effective sample size; HR, hazard ratio; H2H, head-to-head; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; R/R, relapsed/refractory; UK, United Kingdom

NICE National Institute for Health and Care Excellence

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

Table 11: Revised Company base case analyses versus alternative BTKis – R/R CLL

	Total costs (£)	Total QALYs	Incremental cost vs. zanubrutinib (£)	Incremental QALY vs. zanubrutinib	ICER (£/QALY) vs. zanubrutinib
Deterministic					
Zanubrutinib	[redacted]	[redacted]	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	0.801	Dominating
Acalabrutinib	[redacted]	[redacted]	[redacted]	1.057	Dominating
Probabilistic					
Zanubrutinib	[redacted]	[redacted]	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	0.759	Dominating
Acalabrutinib	[redacted]	[redacted]	[redacted]	0.886	Dominating

BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; R/R, relapsed/refractory.

Table 12: Key scenario analyses versus alternative BTKis – R/R CLL

Scenario	ICER (£/QALY) vs. acalabrutinib		ICER (£/QALY) vs. ibrutinib	
	Deterministic	Probabilistic	Deterministic	Probabilistic
Base Case	Dominating	Dominating	Dominating	Dominating
PFS curve for zanubrutinib and ibrutinib (Gompertz)	Dominating	Dominating	Dominating	Dominating
PFS curve for zanubrutinib and ibrutinib (Log-normal)	Dominating	Dominating	Dominating	Dominating
OS curve for zanubrutinib and ibrutinib (Exponential)	Dominating	Dominating	Dominating	Dominating
OS curve for zanubrutinib and ibrutinib (Log-normal)	Dominating	Dominating	Dominating	Dominating
Cost-utility (acalabrutinib MAIC 1 ELEVATE-RR)	Dominating	Dominating	N/A	N/A
Cost-utility (acalabrutinib MAIC 1 ASCEND)	£4,509,840 (SW)*	£1,508,854 (SW)*	N/A	N/A
Cost-utility (acalabrutinib MAIC 2 ASCEND)	£389,543 (SW)*	£370,974 (SW)*	N/A	N/A
ALPINE trial-based utilities	Dominating	Dominating	Dominating	Dominating
TA689 utilities (PF = 0.78; PD = 0.60)	Dominating	Dominating	Dominating	Dominating

BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; R/R, relapsed/refractory; TTD, time to treatment discontinuation. *An ICER in the SW is assessed via an inverted threshold, such that an ICER > £30,000 can be considered cost-effective.

7	**Cost-utility analysis versus fixed-duration therapies – R/R CLL**

Please return to: **NICE DOCS**

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

As outlined in Comment 2, the Company maintain that a comparison with fixed-duration therapy, namely VenR, is not relevant to this NICE appraisal given that zanubrutinib is positioned as an alternative BTKi treatment and the introduction of zanubrutinib will not impact the clinical decision of whether to prescribe a fixed-duration or continuous treatment as supported by consensus statements obtained from a Delphi panel conducted with 11 UK clinical experts.[1]

Nevertheless, to alleviate concerns presented by the Committee in the ACD, the Company have conducted an exploratory cost-effectiveness analysis versus VenR in patients with R/R CLL. The Company's existing economic model for patients for R/R CLL was adapted to include VenR as a comparator. The model settings, data sources and the assumptions presented in Table 10 are also applicable to this comparison. A summary of settings specific to VenR is presented in Table 13.

Exploratory base case results are presented in Table 14, with key scenario analyses presented in Table 15. In the base-case analysis, zanubrutinib is less costly and less effective than VenR, generating a SW quadrant ICER of £440,995. In the SW quadrant the willingness-to-pay (WTP) threshold inverts, meaning that under the base-case settings zanubrutinib can be considered a cost-effective treatment option versus VenR at a WTP threshold of £30,000. Across all scenario analyses performed (addressing the uncertainty of survival assumptions, subsequent treatment and utility sources), zanubrutinib remains cost-effective in the SW quadrant versus VenR for patients with R/R CLL. Mean probabilistic costs and QALYs lie close to the deterministic results for the base case setting and across all scenario analyses, demonstrating the robustness of the Company's analyses.

Table 13: Summary of model settings for comparisons with fixed-duration therapies – R/R CLL

Setting	Updated Company base case	Notes
Comparators	VenR: Patients with R/R CLL.	As per NICE recommendation
Comparative efficacy	VenR: Published NMA (Chanan-Khan 2022)[19]	As published evidence was available to inform the comparative efficacy of zanubrutinib and VenR, additional analyses were not conducted due to time constraints. The trial data to inform the published NMA is aligned with the DCO used in the models for zanubrutinib, ibrutinib and acalabrutinib (ALPINE 2021 DCO). The results of the NMA indicate that zanubrutinib is numerically favoured for PFS (HR: 0.69 [95% CI 0.32,

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

		1.46]), whilst VenR is numerically favoured for OS (HR: 1.27 [95% CI 0.47, 3.33]). It is important to note that the number of prior lines of treatment in MURANO was limited to a maximum of 3, while ALPINE had no upper limit on the number or prior treatment lines. This means that the ALPINE population is more heavily pre-treated (range of prior lines was between 1 and 6) with a potentially poorer survival prognosis, which may have contributed to the flip of effect between the PFS and OS HRs. The NMA is subject to uncertainty given that the network is linked through ELEVATE-RR which only enrolled high-risk R/R patients.
PFS modelling	VenR: PFS HR (Published NMA [HR: 0.69; 95% CI: 0.32, 1.46]) applied to extrapolated zanubrutinib curve.	Methodology in line with comparisons with alternative BTKis.
OS modelling	VenR: OS HR (Published NMA [HR: 1.27; 95% CI: 0.47, 3.33]) applied to extrapolated zanubrutinib curve.	Methodology in line with comparisons with alternative BTKis.
Subsequent treatment modelling	100% acalabrutinib after first-line Ven-based treatment. A scenario analysis considered a proportion of patients may also receive idelalisib-rituximab after progression on VenR.	Reflects subsequent treatment pathway in clinical practice and clinical guidelines for treatment sequencing, as validated by UK clinical experts in attendance at Delphi panel.
Safety modelling	AE rates from MURANO.	Methodology in line with comparisons with alternative BTKis.

AE, adverse events; BTKi, Bruton Kinase inhibitors; CLL, chronic lymphocytic leukaemia; HR, hazard ratio; NMA, network meta-analysis; NICE, National Institute for Health and care Excellence; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TTD, time to treatment discontinuation; VenR, venetoclax-rituximab.

Table 14: Exploratory Company analyses with fixed-duration therapies – R/R CLL

	Total costs (£)	Total QALYs	Incremental cost vs. zanubrutinib (£)	Incremental QALY vs. zanubrutinib	ICER (£/QALY) vs. zanubrutinib
Deterministic					
Zanubrutinib	[redacted]	[redacted]	-	-	-
VenR	[redacted]	[redacted]	[redacted]	-0.330	440,995 (SW)*
Probabilistic					
Zanubrutinib	[redacted]	[redacted]	-	-	-

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Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

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VenR	[redacted]	[redacted]	[redacted]	-0.396	344,075 (SW)*

CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio, quality-adjusted life year; R/R, relapsed/refractory; VenR, venetoclax-rituximab. *An ICER in the SW is assessed via an inverted threshold, such that an ICER > £30,000 can be considered cost-effective.

Table 15: Key scenario analyses with fixed-duration therapies – R/R CLL

Scenario	ICER (£/QALY) vs. VenR	
	Deterministic (£)	Probabilistic (£)
Base Case	440,995 (SW)*	324,191 (SW)*
PFS curve for zanubrutinib (Gompertz)	440,858 (SW)*	333,735 (SW)*
PFS curve for zanubrutinib (Log-normal)	313,972 (SW)*	246,768 (SW)*
OS curve for zanubrutinib (Exponential)	422,538 (SW)*	334,536 (SW)*
OS curve for zanubrutinib (Log-normal)	925,561 (SW)*	701,812 (SW)*
80%:20% BTKi: Idelalsib-rituximab after progression on VenR	377,057 (SW)*	281,749 (SW)*
ALPINE trial-based utilities	260,169 (SW)*	224,859 (SW)*
TA689 utilities (PF = 0.78; PD = 0.60)	490,271 (SW)*	317,781 (SW)*

CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS , progression-free survival; QALY, quality-adjusted life year; R/R, relapsed/refractory; TTD, time to treatment discontinuation; VenR, VenO, venetoclax-rituximab. *An ICER in the SW is assessed via an inverted threshold, such that an ICER > £30,000 can be considered cost-effective.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Point 3.2 on the clinical management of CLL also highlights comments from the patient expert on treatment options. We wanted to add an additional comment on increasing treatment options.

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Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

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	Some patients prefer to take a continuous duration treatment as it provides them with regular reassurance because they feel they are keeping on top of their disease with medication consistently. This can help to reduce anxiety of possible disease progression in some patients. Furthermore, many treatments of a fixed duration can be quite intensive and dose escalation schedules and protocols can be demanding on the patient, who might need to travel to hospital regularly. Single agent continuous BTKis, like zanubrutinib, can reduce the need for in hospital attendance. Similarly, a single agent BTKi reduces the need for hospital attendance for IV components in both the first and second line (e.g., obinutuzumab and rituximab). It is important that patients with CLL have as many treatment options available to them as possible and that those treatments offer different characteristics, e.g., method of delivery and duration, so that clinicians can provide personalised treatment plans which suit individual patients and their lifestyles. Zanubrutinib, if approved, should be available in all relevant subgroups and cohorts in CLL.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK CLL Forum British Society for Haematology Royal College of Pathologists

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Please state:
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• the amount
• the purpose of funding including whether it related to a product mentioned in the stakeholder list
• whether it is ongoing or has ceased.</td><td>UK CLL Forum - support received for meetings 01/08/22- 01/08.23

<table><tr><td>Roche</td><td>£4,500.00</td></tr><tr><td>BeiGene</td><td>£10,000.00</td></tr><tr><td>AbbVie</td><td>£14,500.00</td></tr><tr><td>Janssen</td><td>£8,800.00</td></tr><tr><td>Adaptive Biotechnologies</td><td>£7,000.00</td></tr><tr><td>AstraZeneca</td><td>£10,000.00</td></tr></table></td></tr>
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<tr><td>Name of commentator person completing form:</td><td>Dr Rosalynd Johnston</td></tr>
</table>

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	As members of the UK CLL Forum executive committee, the British Society of Haematology and the Royal College of Pathologists, we are concerned that the provisional recommendations in this draft guidance do not represent the most suitable guidance for the NHS. We are happy with the evidence base used, but are concerned that the difficulties of statistically modelling and extrapolating short-term follow-up data, with low event numbers for key survival outcomes, has potentially disadvantaged the appraisal of this well-tolerated and efficacious therapy.

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2	Zanubrutinib is a safe and effective BTKi with a favourable efficacy and side effect profile when compared with Ibrutinib, particularly in relation to serious cardiac events. No direct comparison with Acalabrutinib is available from clinical trials in untreated or relapsed/ refractory CLL. As stated at the end of section 3.10 of the draft guidance, "the available evidence for Zanubrutinib suggests a toxicity profile better than Ibrutinib and similar or better than Acalabrutinib".
3	Chemo-immunotherapy (FCR/BR) is no longer a standard of care in any setting for CLL patients. All available targeted therapies (any single agent or combination containing BTKi and/or Venetoclax) have proven efficacy in the population previously considered "unfit" for certain chemotherapy regimes meaning that the historical differentiation between "fit" and "unfit" patients is now redundant.
4	Inequality of access to continuous BTKi therapy exists in the UK, in the untreated CLL population. Younger, fitter patients who have an intact p53 gene are unable to access this treatment modality. This technology appraisal offers the opportunity to redress this using the SEQUOIA data, where patients were deemed to be "fit" to be randomised to Bendamustine and Rituximab chemo-immunotherapy in the trial.
5	Ven-O, Ven-Ibr (upfront) and Ven-R (relapse/refractory) are NICE approved treatment options for patients with CLL and we agree that they are relevant comparators for Zanubrutinib. Importantly, however, these Venetoclax-based regimens are time-limited, unlike the continuous BTKi regimens. Zanubrutinib sits as an alternative BTKi in both settings. The availability of Zanubrutinib is unlikely to impact significantly on the clinical decision to treat with a time-limited vs a continuous treatment regime. In this respect, the most important comparators to Zanubrutinib are the other continuous BTKi regimens currently available; Acalabrutinib and Ibrutinib.
6	Furthermore, the majority of patients are likely to cycle through both time-limited Venetoclax based regimes as well as continuous BTKi based regimes in their treatment lifetime. Availability of Zanubrutinib would give access to a cost-effective and efficacious alternative to Acalabrutinib or Ibrutinib; and give choice in navigating different adverse events; rather than an additional line of therapy.
7	Although Venetoclax plus Ibrutinib is a now a comparator in the upfront setting, we feel the utility of direct comparison with Zanubrutinib monotherapy is likely to be limited by the small numbers of patients in the GLOW and CAPTIVATE studies; short follow-up and the current uncertainties around the optimal treatment at relapse in those who receive Venetoclax and Ibrutinib first line. In addition, a significant cardiac signal remains in the GLOW study and we await real-world data around this to complement our clinical decision–making. It is difficult to model the cost, long-term health impact and implications for future therapy of acquiring, for example, atrial fibrillation during time-limited therapy with Venetoclax and Ibrutinib which will persist, likely for the rest of the patient's life, rather than resolving at the end of 15 months of treatment. This important data is currently absent. In summary, there is currently comparison between any of the available therapies from randomised trials to guide choice of therapy in the upfront setting.
8	There comments have been collated and reviewed by the following clinical experts; Dr Rosalynd Johnston, University Hospitals Sussex; [redacted]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable – no disclosures
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Venetoclax-based treatment regimens are important treatment options in both untreated and relapsed/refractory chronic lymphocytic leukaemia.

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Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 22 August 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Janssen Cilag Ltd.

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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 • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	Janssen Cilag Ltd.

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**1L CLL population (previously untreated)**: While we welcome additional treatment options for CLL patients in England and Wales to enable patients to receive the best suitable treatments, we are concerned about the comparisons presented for zanubrutinib in the fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) unsuitable previously untreated chronic lymphocytic lukaemia (CLL) population. Limitations of the evidence base make it difficult to reach some of the firm conclusions currently presented in the draft guidance.

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	Given that the SEQUOIA trial was a head-to-head comparison with BR, we agree with the EAG that it means patients had to be 'eligible for BR' to even participate in the study. Eligibility for BR is mostly a consideration of patients' ability to tolerate BR, and historically patients who were not seen as eligible for BR would receive alternatives with a more favourable toxicity profile. All novel therapies assessed by NICE so far have presented evidence from head-to-head studies vs obinutuzumab plus chlorambucil (O-Clb) to establish efficacy. Although some indirect techniques can be employed to produce efficacy and safety comparisons their interpretation will be problematic since inherently patients eligible for BR are expected to perform better than those who are not, especially with respect to tolerability, so outcomes will be biased in favour of Zanubrutinib. **Such comparisons are highly uncertain and cannot be deemed informative for establishing the relative clinical benefit, cost-savings and utility improvements associated with the FCR/BR unsuitable patient population.**
2	**High-Risk RR Population**: We are concerned with the applicability of the randomised controlled trial (RCT) presented for the relapsed refractory (RR) CLL population to the decision problem. This study is an outlier in the body of evidence for the efficacy of ibrutinib in RR CLL patients, and severely underperforms compared to ibrutinib's registrational study despite including less pre-treated patients; the evidence presented to NICE is not in line with the body of existing available evidence. Please see additional data presented in an abstract from European Haematology Association HERE). Furthermore, the statistically significant progression free survival (PFS) benefit presented by the submitting company in the zanubrutinib appraisal is driven by patients outside of Europe which increases the uncertainty about certainty of this PFS advantage materialising in England and subsequently outcomes of modelling presented by the Company.
3	**High-Risk Population Extrapolation in 1L**: The use of RR CLL data in the high-risk population as a proxy to first-line (1L) CLL patient setting is clinically and methodologically concerning and should be interpreted with caution. While it was acceptable when the first targeted agents entered treatment pathway due to limited evidence, it is unclear whether the Company reviewed the available evidence before concluding RR CLL data in the high-risk population should be used as a proxy to 1L CLL. Bruton Tyronsine Kinase inhibitors' (BTKi's) have been used in the 1L setting for more than 5 years in many countries globally and some data does exist. For example, Allan et al. (Br J Haemtolo 2022) published data for a cohort of 89 patients pooled from 1L CLL trials with ibrutinib regimen trials.
4	**Factual Inaccuracy/Clarification – Section 3.4. - Page 7** "*The company submission highlighted the lower hazard ratio with narrower confidence intervals from a later data cut (8 August 2022). This highlighted that the difference in the **number of deaths** between zanubrutinib and ibrutinib further increased, suggesting that a statistically significantly improvement in OS may be demonstrated with more mature data."* Janssen want to highlight an inaccuracy in the draft guidance: When reporting results of clinical trials in oncology, it is common practice to express survival benefit based on the hazard ratio (HR) from a survival analysis as a "reduction in the risk of death," by an amount equal to 100 × (1 − HR) %. Hence, HR is not translatable to number of deaths.

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	It is not appropriate translate hazard ratios to deaths as the lower hazard ratio does not in fact highlight the difference in deaths between zanubrutinib and ibrutinib, and we therefore suggest this sentence is removed as it is not an appropriate assumption to make. Furthermore, while we appreciate this may be the stated position of the company, a statistical difference is still yet to be demonstrated and mature data is not, in fact, available. Therefore, any conclusion is a hypothesis only. We are concerned that this will be interpreted by the reader as what would likely happen without evidence to back this up.
5	**Factual Inaccuracy /Clarification – Section 3.10. - Page 13** *"There were no deaths because of cardiac disorders with zanubrutinib whereas ibrutinib was associated with deaths related to adverse cardiovascular events. The clinical experts agreed that the available evidence for zanubrutinib suggests a toxicity profile better than ibrutinib, and similar or better than acalabrutinib. The committee concluded that zanubrutinib is a tolerable and safe treatment for previously untreated CLL and relapsed or refractory CLL."* Janssen would like to highlight that all BTKis have similar known events as there is a clinically known class effect of BTKis. Overall, a lower incidence of cardiac disorders was reported in the zanubrutinib group (21.3%) than in the ibrutinib group (29.6%), so the results are anticipated based on the differences in baseline characteristics of patients. In the ibrutinib group, cardiac disorders leading to treatment discontinuation occurred in 1 patient (0.3%). However, in the zanubrutinib group and 14 patients (4.3%). Six deaths due to cardiac events were reported, all in patients who received ibrutinib. Of the 6 patients who died, 3 died within 4 months after the initiation of ibrutinib, and **all these patients had cardiac coexisting conditions**. The other three deaths occurred 2 to 3 years after the initiation of ibrutinib, one in a patient who did not have a history of cardiac disorders. We would therefore note that the text included by NICE is a misrepresentation of the evidence without further context. The paragraph also reads as though there are no cardiac events with zanubrutinib, which again due to the BTKi class effect, is not the case. We welcome the expertise and contribution to the NICE process of the clinical experts; we believe that this should be interpreted alongside the data available; the way in which the evidence has been written in the draft guideline however, is not reflective of the evidence base as described above.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the

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following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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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Single Technology Appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

How did Acalabrunib get a "pass" on so many of the same things that are given as reasons to not recommend Zanubrutinib?

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Unknown but based on list prices without access to NHS prices Zanubrutinib is more effective but less tolerated than Acalabruntinib. If recommended it would be first choice for many patients.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The lack of invalid comparisons of a long term BTKi therapy to short duration Venetoclax BCL-2 therapies has been repeatedly cited as reasons to not recommend.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No.

As 1st line

1: You ask for comparisons to short duration Venetoclax + Obinutuzumab (VenO) and Ibrutinib + Venetoclax (I+V). Zunubrutinib mono-therapy is a long duration treatment that competes with other BTKi mono-therapy drugs and not short duration treatments. The selection of short duration or long term treatment is at patients and consultants discretion, steered by patients co-morbidities such as heart and kidney condition. In link (below) to NHS treatment algorithm at St Lukes (Royal Surrey) it can be seen that VenO and BTKi are two separate distinct treatment arms. The doctor and patient have weigh up the choice between a short intense treatment that offers a treatment free period or a long term BTKi with potential longer time to progression. I+V will fit on this algorithm on the centre arm alongside VenO as a less intense but slightly longer short duration treatment.

https://www.royalsurrey.nhs.uk/download.cfm?doc=docm93jijm4n18027.pdf&ver=45582

2: Short duration therapies tend to have shorter time to progression after end of of treatment. This is countered by having more 2nd/3rd/4th line treatments that may if lucky offer an overall longer overall survival.

3: You ask for comparisons to the recently approved Ibrutinib + Venetoclax. This is disingenuous as the vendor of Zanubrutinib would not have known they needed to include this when setting up trials 4 or 5 years ago and had no access to the NICE development data for V+I.

4: Agree Zanubrutinib does need to be available to IGVH mutated and wildtype TP53. People are afraid of "chemo" and given other choices will reject it. Acalabrutinib was approved for all without much evidence.

As 2nd line.

2nd line treatment algorithm, see the St Lukes link above or this more extensive algorithm from Clatterbridge CC.

https://www.clatterbridgecc.nhs.uk
/application/files/3516/8561/6870/CCL_Relapsed_Refractory.pdf

1: You ask for comparison to Venetoclax + Rituximab. This isn't a comparable treatment to continuous BTKi mono-therapy. Again it's short duration. As you see from the 2 algorithms presented here it can precede or follow a 3rd/2nd line of BTKi when the patient has had a short duration Venetoclax based 1st line and is not R/R to BTKi drugs. For patients that are R/R after long term 1st line BTKi, VenR is the only choice. For patients that have along enough PFS it may be used as re-treatment.

2: As an option for patients that are not R/R but have tolerance problems with other BTKi drugs it may offer a means to stay on long term 1st line BTKi although considered a 2nd line to the initial BTKi drug. (But if approved is more likely to be Zanu > Acala than the other way round unless already started on Acala)

Additional 1st line comments from this link
https://www.uptodate.com/contents/image?imageKey=HEME%2F122052&topicKey=HEME%2F83749&source=see_link

"If the goal is best efficacy with acceptable tolerability, we offer zanubrutinib. If the goal is best tolerability with good efficacy, we offer acalabrutinib."

"In patients with del17p or TP53 mutation, continuous acalabrutinib or zanubrutinib may be preferred over fixed duration venetoclax plus obinutuzumab based on cross-trial comparisons that suggest decreased efficacy of the latter in this population."

Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]

Produced by	Newcastle University
Authors	Giovany Orozco-Leal, Research Associate, Newcastle University Eugenie Evelynne Johnson, Research Assistant, Newcastle University Nick Meader, Principal Research Associate, Newcastle University Claire Eastaugh, Research Assistant, Newcastle University Sonia Garcia Gonzalez-Moral, Research Associate, Newcastle University Tumi Sotire, Research Assistant, Newcastle University Tara Homer, Senior Research Associate, Newcastle University
Correspondence to	Tara Homer, Newcastle University Baddiley Clark Building, Newcastle University, Newcastle upon Tyne NE2 4BN
Date completed	31/08/2023

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Declared competing interests of the authors

None.

Acknowledgements

Luke Vale, Professor, Newcastle University reviewed the EAG response.

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.

This report should be referenced as follows:

Orozco-Leal G, Johnson EE, Meader N, Eastaugh C, Garcia Gonzalez-Moral S, Sotire T, Homer T. Zanubrutinib for treating chronic lymphocytic leukaemia [ID5078]: a single technology appraisal. Newcastle upon Tyne: Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University; 2023.

Contributions of authors

Tara Homer acted as project lead and health economist reviewer on this assessment, critiqued the clinical effectiveness and economic evaluation methods and evidence, and contributed to the writing of the report. Giovany Orozco-Leal acted as lead health economist, critiqued the company's economic evaluation and contributed to the writing of the report. Eugenie Evelynne Johnson and Nick Meader critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Claire Eastaugh and Sonia Garcia Gonzalez-Moral critiqued the search methods in the submission and contributed to the writing of the report. Tumi Sotire acted as a health economist and contributed to the critique of the company's economic evaluation.

Abbreviations

ACD	Appraisal Committee Document
AE	Adverse event
BR	Bendamustine-rituximab
BTKi	Bruton tyrosine kinase inhibitor
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CIT	Chemoimmunotherapy
CLL	Chronic lymphocytic leukaemia
CLL-IPI	Chronic lymphocytic leukaemia - international prognostic index
CrI	Credible Intervals
CS	Company submission
CUA	Cost-utility analysis
DCO	Data cut-off
del 11q	Deletion of the long arm of chromosome 11
del 13q	Deletion of the long arm of chromosome 13
del 17p	Deletion of the short arm chromosome 17
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status Scale
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
ESS	Effective sample size
FCR	Fludarabine, cyclophosphamide and rituximab
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IGHV	Immunoglobulin heavy chain gene
INV	Investigator
I-R	Idelalisib plus rituximab
IRC	Independent Review Committee
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
I-V	Ibrutinib plus venetoclax
L	Litre
LDi	Longest diameter
MAIC	Matching-adjusted indirect comparison
mg	Milligram
ml	Millilitre
NE	Not evaluated
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PF	Progression-free

PFS	Progression-free survival
PH	Proportional hazard
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk; Risk ratio
R/R	Relapsed or refractory
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
STA	Single technology appraisal
SLL	Small lymphocytic lymphoma
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
UK	United Kingdom
URL	Uniform resource locator
VAS	Visual analogue scale
VenO	Venetoclax-obintutuzumab
VenR	Venetoclax-rituximab
1LTx	First-line treatment
2LTx	Second-line treatment

Table of Contents

Table of Tables

Table of Figures

No table of figures entries found.

1 Overview

The company response to the Appraisal Committee Document (ACD) included updated economic models with eight new analyses presented, four of which had comparators that were not considered in the company submission (CS).[1] The company presented the following evidence:

- Cost-utility analysis (CUA) of zanubrutinib compared with acalabrutinib in the untreated chronic lymphatic leukaemia (CLL) population with or without deletion of the short arm chromosome 17 (del 17p) and/or tumour protein P53 gene (TP53) mutation for whom fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine-rituximab (BR) is unsuitable;
- CUA of zanubrutinib compared with acalabrutinib in the relapsed/refractory (R/R) CLL population;
- CUA of zanubrutinib compared with ibrutinib in the untreated CLL population with del 17p and/or TP53 mutation;
- CUA of zanubrutinib compared with ibrutinib in the R/R CLL population;
- CUA of zanubrutinib compared with ibrutinib plus venetoclax (I-V) in older patients with and without comorbidities in untreated CLL;
- CUA of zanubrutinib compared with I-V in younger patients without comorbidities in untreated CLL;
- CUA of zanubrutinib compared with venetoclax and obinutuzumab (VenO) in the untreated CLL population with or without del 17p and/or TP53 mutation for whom FCR or BR is unsuitable;
- CUA of zanubruitib compared with venetoclax plus rituximab (VenR) in the R/R CLL population.

The company maintained the view that the existing economic models used in the original CS were sufficient to address the research question hence they made no structural or functional changes except removing the assumption of equivalent effectiveness.

The company used the latest data cuts from the SEQUOIA trial to update the matching-adjusted indirect comparisons (MAICs) to inform the clinical data comparing acalabrutinib and ibrutinib with zanubrutinib in the untreated CLL populations. The company used the latest data cut from ALPINE to update the comparison of zanubrutinib with ibrutinib in the 'high-risk' untreated CLL population. The company used the latest data cut from the ALPINE trial to validate the survival extrapolations comparing zanubrutinib with ibrutinib in R/R CLL but did not incorporate these data into the economic model.

To estimate outcome data for the new comparators VenO and I-V in previously untreated CLL, the company undertook three MAICs. The methods used were the same as reported in the CS.[1] To estimate outcome data for VenR in R/R CLL, the company used the results of a previously published network meta-analysis (NMA).[2]

The EAG had very little time to review this evidence and so this document is intended to focus on the most important aspects of the company response and identify where there is still uncertainty surrounding the effectiveness and cost-effectiveness of zanubrutinib.

1.1 Clinical study results ACD Section 3.4, p6-7.

Results for key clinical outcomes from the latest data cut for both SEQUOIA and ALPINE may better inform the long-term effectiveness of zanubrutinib for all CLL populations.

1.1.1 SEQUOIA results

In their response to the ACD, the company have provided summaries of the latest data cuts for SEQUOIA at a median follow-up time of [redacted] in Cohort 1 (zanubrutinib versus BR) and [redacted] in Cohort 2 (zanubrutinib alone).[3] The latest data cut from SEQUOIA was incorporated into the company's economic models and the following MAICs were conducted:

- zanubrutinib versus I-V (using the GLOW study; see Section 1.3.2.1.1);
- zanubrutinib versus I-V (using the CAPTIVATE study; see Section 1.3.2.1.2);
- zanubrutinib versus VenO (using the CLL14 trial; see Section 1.3.1.1); and
- zanubrutnib versus acalabarutinib and ibrutinib (see Section 1.5).

Comparisons between previous data cut-offs (DCOs) and updated data for investigator-assessed progression-free survival (PFS) and overall survival (OS) are presented in Table 1.1, overall adverse events (fAEs) are reported in Table 1.2 and rates of Grade 3+ treatment-emergent adverse events (TEAEs; > 2% in either arm) in Table 1.3.

Table 1.1: Comparison of updated SEQUOIA efficacy data with previous data cut-offs

Outcome	DCO 31 October 2022			DCO 7 May 2021			DCO 7 March 2022 (OS only)		
	Cohort 1		Cohort 2	Cohort 1		Cohort 2	Cohort 1		Cohort 2
	Zanubrutinib	BR	Zanubrutinib	Zanubrutinib (N=241)	BR (N=238)	Zanubrutinib (N=110)	Zanubrutinib (N=241)	BR (N=238)	Zanubrutinib (N=110)
INV assessed PFS									
N events (%)	[redacted]	[redacted]	[redacted]	29 (12.0)	57 (23.9)	[redacted]	-	-	-
Median (95% CI)	[redacted]	42.2 [redacted]	[redacted]	-	-	-	-	-	-
HR (95% CI)	0.30 (0.21, 0.43)		-	0.42 (0.27, 0.66)		-	-	-	-
Nominal P value	<0.0001		-	p<0.0001		-	-	-	-
OS									
N events (%)	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]	[redacted]	-
Median (95% CI)	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
HR (95% CI)	0.87 (0.50, 1.48)			-	-	-	[redacted]		-
Nominal P value	[redacted]			-	-	-	[redacted]		-

Created by the EAG
Source: Company response to ACD (Appendix 1, Tables 1 and 2);[3] original CS (Section B.2a.6.1, Table 19, p.62; Section B.2a.6.3, p.65; Section B.2a.6.4, Table 26, p.71; Section B.2a.6.4, Table 28, p.73)[1]
Abbreviations: ACD = Appraisal Committee Document; BR = bendamustine-rituximab; CI = confidence interval; DCO = data cut-off; EAG = Evidence Assessment Group; HR = hazard ratio; INV = investigator; NE = not evaluated; OS = overall survival; PFS = progression-free survival.

Table 1.2: Comparison of updated SEQUOIA overall safety data with previous data cut-offs

Oucome (n, %)	DCO 7 May 2022			DCO 7 May 2021		
	Cohort 1		Cohort 2	Cohort 1		Cohort 2
	Zanubrutinib (N = 240)	BR (N = 227)	Zanubrutinib (N = 111)	Zanubrutinib (N = 240)	BR (N = 227)	Zanubrutinib (N = 111)
Patients with at least 1 AE (TEAEs >10% in either arm)	[redacted]	[redacted]	[redacted]	224 (93.3)	218 (96.0)	109 (98.2)
Patients with at least one Grade 3+ TEAE post-treatment (AE > 2% in either arm)	[redacted]	[redacted]	[redacted]	126 (52.5)	181 (79.7)	61 (55.0)

Created by the EAG
Source: Company response to ACD (Appendix 1, Tables 4 and 5);[3] original CS (Section B.2a.10.2, Tables 61 and 62, p.148-50)[1]
Abbreviations: ACD = Appraisal Committee Document; BR = bendamustine-rituximab; CI = confidence interval; DCO = data cut-off; EAG = Evidence Assessment Group; HR = hazard ratio; INV = investigator; NE = not evaluated; OS = overall survival; PFS = progression-free survival.

Table 1.3: Most frequent Grade 3+ TEAEs and post-treatment AEs (> 2% in either arm) in SEQUOIA (DCO: 31 October 2022)

AE by Preferred Term	Cohort 1		Cohort 2
	BR (N=227)	Zanubrutinib (N=240)	Zanubrutinib (N=111)
Patients with at least one TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Benign prostatic hyperplasia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]

Source: Company response to ACD (Appendix 1, Table 5)[3]
Abbreviations: ACD = Appraisal Committee Document; AE = adverse event; BR = bendamustine-rituximab; DCO = data cut-off; TEAE = treatment-emergent adverse event.

To facilitate comparison between the Grade 3+ TEAEs and post-treatment AEs presented in Table 1.3, the Grade 3+ TEAEs and post-treatment AEs for the DCO on 7 May 2021 are presented in Table 1.4.

Table 1.4: Grade 3+ TEAEs and post-treatment AEs reported in ≥2% of patients in either arm in SEQUOIA in the CS

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 (Section B.2a.10.2, Table 62)[1]
Abbreviations: AE = adverse event; BR = bendamustine-rituximab; CS = company submission; TEAE = treatment-emergent adverse event.

The untreated CLL economic model accounted for cardiac related AEs by including costs and disutilities for atrial fibrillation and cardiac failure. In the zanubrutinib arm, AEs probabilities were informed using SEQUOIA, while RESONATE-2, ELEVATE-TN, CLL14, and GLOW plus CAPTIVATE were used to inform the ibrutinb, acalabrutinib, VenO and I-V comparator arms respectively.[4]

EAG comment: It is unclear to the EAG whether cardiac failures were recorded for any participants in SEQUOIA as only an updated table of Grade 3+ TEAEs was provided in the company response to the ACD.[4] The EAG confirmed in the untreated CLL model that no cardiac failures were included for the BTKi treatments, but they were for the venetoclax-based treatments.

The need to include multiple trials to inform the AEs on each arm leads to a possible underestimation of I-V AEs as the inclusion criteria for the source data was narrower (Grade 3+ AEs occurring in ≥ 5% of patients) than those reported in SEQUOIA (Grade 3+ AEs occurring in ≥ 2% of patients).[3] Moreover,

it is unclear whether the definition of diarrhoea and infectious AEs included for the VenO and I-V arms match the AEs recorded in SEQUOIA, since the model does not include sepsis or urinary tract infection events in this category.

The EAG response on how these AEs were incorporated into the untreated CLL model is provided in Sections 1.6.3 and 1.9.

1.1.2 ALPINE results

The company presented updated data from the ALPINE trial taken from the 15 May 2023 DCO, with a follow-up time of [redacted] (company response to ACD, Appendix 2).[3] However, the company stated that these data were not included in the R/R CLL economic model and were instead used by the company to validate the choice of survival extrapolations (company response to ACD, Appendix 2).[3] This is discussed in further detail in Section 1.7.

Comparisons between previous DCOs and updated data for investigator-assessed overall response rate (ORR), investigator-assessed PFS and OS are presented in Table 1.5 and overall AEs are reported in Table 1.6.

Table 1.5: Comparison of updated ALPINE efficacy data with previous data cut-offs

Outcome	DCO: 15 May 2023		DCO: 1 December 2021		DCO: 8 August 2022	
	Zanubrutinib	**Ibrutinib**	**Zanubrutinib (N=327)**	**Ibrutinib (N=325)**	**Zanubrutinib (N=327)**	**Ibrutinib (N=325)**
ORR by INV						
By arm	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Response ratio	[redacted]		[redacted]		-	-
Complete response rate	[redacted]	[redacted]	[redacted]	[redacted]	-	-
INV-assessed PFS						
All participants						
Number of events (%)	[redacted]	[redacted]	[redacted]	[redacted]	87 (26.6)	118 (36.3)
HR (95% CI):	[redacted]		[redacted]		0.65 (0.49, 0.86)	
Nominal P-value	[redacted]		[redacted]		0.0024	
Patients with 17p deletion or TP53 deletion						
Number of events (%)	[redacted]	[redacted]	-	-	-	-
HR (95% CI):	[redacted]		[redacted]		-	
OS						
Number of events (%)	[redacted]	[redacted]	[redacted]	[redacted]	-	-
HR (95% CI):	[redacted]		[redacted]		0.76 (0.51, 1.11)	
Nominal P-value	[redacted]		[redacted]		-	-

Created by the EAG
Source: Company response to ACD Appendix 2 (Overall response rate text; Tables 6 and 7);[3] original CS (Section B.2b.6, Table 35, p.85-6; Section B.2b.6.1, Table 36, p.87; Section B.2b.6.3, Table 38, p.91-2; Section B.2b.6.3, p.95; Section B.2b.6.3, Table 41, p.96)[1]
Abbreviations: ACD = Appraisal Committee Document; CI = confidence interval; DCO = data cut-off; EAG = Evidence Assessment Group; HR = hazard ratio; INV = investigator; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Table 1.6: Comparison of updated ALPINE overall safety data with previous data cut-offs

Outcome	**DCO: 15 May 2023**		**DCO: 1 December 2021**	
	Zanubrutinib (N = 324)	**Ibrutinib (N = 324)**	**Zanubrutinib (N = 324)**	**Ibrutinib (N = 324)**
Patients with at least 1 AE (TEAEs >10% in either arm)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one Grade 3+ TEAE post-treatment (AE > 1% in either arm)	[redacted]	[redacted]	[redacted]	[redacted]

Created by the EAG
Source: Company response to ACD Appendix 2 (Tables 9 and 10);[3] original CS (Section B.2b.10.2, Tables 64 and 65, p.154-5)[1]
Abbreviations: ACD = Appraisal Committee Document; AE = adverse event; DCO = data cut-off; EAG = Evidence Assessment Group; TEAE = treatment-emergent adverse event.

Table 1.7 summarises the number of Grade 3+ TEAEs (> 2% in either arm) reported by the company in their response to the ACD.[4]

Table 1.7: Most frequent Grade 3+ TEAEs (> 2% in either arm) in ALPINE

AE by Preferred Term	Zanubrutinib (N=324)	Ibrutinib (N=324)
Patients with at least one TEAE	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Petechiae	[redacted]	[redacted]

Source: Company response to ACD (Appendix 2, Table 10)[3]
Abbreviations: ACD = Appraisal Committee Document; AE = adverse event; DCO = data cut-off; TEAE = treatment-emergent adverse event.

For comparison, Grade 3+ TEAEs reported in the prior DCO (1 December 2021) for ALPINE are reported in Table 1.8.

Table 1.8: Grade 3 or higher TEAEs in ≥1% in either arm in ALPINE as reported in the CS

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		

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
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]
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 (Section B.2b.10.2, Table 65)[1]
Abbreviations: CS = company submission; TEAE = treatment-emergent adverse event.

The cardiac events in ALPINE are shown in Table 1.9. In their response to the ACD the company specified the cardiac events that led to treatment discontinuation and death (Appendix 2, Table 11).[3]

Table 1.9: Cardiac events in ALPINE

	Zanubrutinib (N=324)	Ibrutinib (N=324)
Patients with any cardiac TEAE	[redacted]	[redacted]
Grade 3 or higher cardiac TEAE	[redacted]	[redacted]
Serious cardiac TEAE	[redacted]	[redacted]

Cardiac TEAE leading to treatment discontinuation	[redacted]	[redacted]
Fatal cardiac TEAE	[redacted]	[redacted]
Source: Company response to ACD (Appendix 2, Table 11)[3] Abbreviations: ACD = Appraisal Committee Document; TEAE = treatment-emergent adverse event.		

EAG comment: The EAG response on how these AEs were incorporated into the R/R CLL model is provided in Sections 1.6.3 and 1.9.

1.2 Untreated CLL population for whom FCR or BR is suitable ACD Section 3.5, p7-8.

People with untreated CLL for whom FCR and BR is suitable, is an important subgroup and evidence from SEQUOIA could be used for this population.

The company acknowledge that the NICE committee considered data from the SEQUOIA trial to be applicable to people with untreated CLL regardless of suitability for FCR or BR.[4] However, the company have not used data from SEQOUIA to compare the effectiveness and cost-effectiveness of zanubrutinib with the other BTKi comparators (acalabrutinib and ibrutinib) or VenO in those with untreated CLL for whom FCR and BR is suitable.

The company have compared zanubrutinib with I-V, using data from younger people without comorbidities. The company undertook a MAIC using data from both SEQUOIA and CAPTIVATE to estimate the effectiveness of zanubrutinib in this population.[4] These data were incorporated into the economic model to estimate the cost-effectiveness of zanubrutinib in this population. Further details of these results are provided in Section 1.3.2.

EAG comment: The EAG is not currently aware whether there are data available on the effectiveness of acalabrutinib, ibruitinub and VenO in people with untreated CLL for whom FCR and BR is suitable. Regardless, the company have not positioned zanubrutinib as a treatment option for this population in these comparisons.

The EAG have provided critique on the MAIC, which estimated the relative effectiveness of zanubrutinib compared with I-V in untreated CLL patients who are elgibile for FCR and BR, in Section 1.3.2.1.2. The EAG critique of the economic model, which estimated the cost-effectiveness of zanubrutinib compared with I-V in this population, is provided in Section 1.3.2.2.

1.3 Untreated CLL population for whom FCR or BR is unsuitable ACD Section 3.6, p8-9.

Additional clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus obinutuzumab and ibrutinib plus venetoclax for the untreated CLL population.

The company maintain their view that zanubrutinib would only be considered as an alternative Bruton's tyrosine kinase inhibitor (BTKi) monotherapy and that fixed-duration therapies (i.e. venetoclax-based regimens) are not relevant comparators. However, to alleviate the concerns of the Committee, the company provided evidence on the clinical and cost-effectiveness of zanubrutinib compared with VenO and zanubrutinib compared with I-V in the untreated CLL population.

1.3.1 Zanubrutinib versus venetoclax plus obinutuzumab

1.3.1.1 MAICs

The company conducted a MAIC using the CLL14 study to estimate comparative efficacy between zanubrutinib and VenO (Company Response to ACD, Appendix 4).[3] Of the published papers surrounding CLL14, the company deemed Al-Sawaf *et al*. (2023) to be most appropriate given it presented the most up-to-date data, with a median follow-up of 76.4 months.[5] The company noted that CLL14 had a longer follow-up period than those in Cohort 1 of SEQUOIA at the 31 October 2022 DCO ([redacted]; Company Response to ACD, Appendix 4).[3] As the baseline characteristics for those with and without 17p deletion were not reported separately in CLL14, the company pooled data from Arm A of Cohort 1 and Cohort 2 (Arm C) of SEQUOIA to create a cohort that included patients with and without 17p deletion to match those in CLL14.

As CLL14 and SEQUOIA did not contain a common comparator arm, an unanchored MAIC was conducted in accordance with the NICE DSU guidelines and methods described by Signorovich *et al*. (2012).[6,7] The company adopted a matching model with covariate adjustment aligned to those matched in the ELEVATE-TN MAIC (Company Response to ACD, Appendix 3).[3] As complex karyotype had a high missing rate in SEQUOIA ([redacted]), it was excluded from the list of matching factors. The largest imbalance between the populations was the proportion of patients with a Cumulative Illness Rating Scale (CIRS) > 6; the company excluded this from the list of covariates to preserve effective sample size (ESS) (Company Response to ACD, Appendix 4).[3] The company noted that the matched model resulted in a sufficiently large ESS (> 100), with covariates aligned to those matched within the ELEVATE-TN MAICs (Company Response to ACD, Appendix 4).[3]

Table 1.10 summarises the population characteristics for both Model 1 and Model 2 after matching by weights.

Table 1.10: Characteristics of VenO population in CLL14 versus zanubrutinib population in SEQUOIA after matching

Population Characteristics		VenO (N = 216)	Zanubrutinib (ESS = 153)
Cytogenetic subgroup as per hierarchy	del17p (vs. del13q), %	8.10%	[redacted]
	del11q (vs. del13q), %	17.10%	[redacted]
	Trisomy 12 (vs. del13q), %	17.10%	[redacted]
	None (vs. del13q), %	23.80%	[redacted]
TP53 mutation	Yes (vs. no), %	12.0%	[redacted]
IGHV mutation	Mutated (vs. unmutated), %	38.60%	[redacted]
β_2-Microglobulin, mg/L	>3.5 (vs. ≤ 3.5), %	59.40%	[redacted]
	Median	3.9	[redacted]
Age, years	≥ 75 (vs. < 75), %	33.30%	[redacted]
	Median	72	[redacted]
Sex	Male (vs. female), %	67.60%	[redacted]
ECOG PS	1 (vs. 0), %	45.80%	[redacted]

	2+ (vs. 0), %	13.00%	[redacted]
Binet stage	B (vs. A), %	35.20%	[redacted]
	C (vs. A), %	43.50%	[redacted]
CLL-IPI	Intermediate (2-3) (vs. Low), %	25.00%	[redacted]
	High (4-6) (vs. Low), %	60.00%	[redacted]
	Very high (7-10) (vs. Low), %	6.00%	[redacted]
Creatinine clearance, mL/min	< 70 (vs. ≥ 70), %	59.50%	[redacted]
	Median	65.2	[redacted]
Complex karyotype (≥3 abnormalities)	Yes (vs. no), %	17.00%	[redacted]
Cancer type	CLL (vs. SLL), %	100.00%	[redacted]
Time from initial diagnosis, months	Median	31.2	[redacted]
B-symptoms	Yes (vs. no), %	48.00%	[redacted]
CIRS	> 6 (vs ≤ 6), %	86.10%	[redacted]

Source: Company response to ACD (Appendix 4, Table 15)[3]
Footnote from Appendix 4, Table 15: Adjusted characteristics are highlighted in green and unadjusted characteristics are highlighted in pink.
Abbreviations: ACD = Appraisal Committee Document; 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; L = litre; mg = milligram; mL = millilitre; PS = performance status; SLL = Small lymphocytic lymphoma; TP53 = Tumour protein P53 gene; VenO = venetoclax and obinutuzumab.

The company stated that the PFS and OS endpoints in SEQUOIA were impacted by COVID-19 deaths (with [redacted] deaths due to COVID-19 related AEs in the zanubrutinib arm), but that the CLL14 would not have experienced this as it was conducted prior to the pandemic. Therefore, the company undertook exploratory analyses in which patients who had died of confirmed COVID-19 in the SEQUOIA dataset were censored at the time of their last tumour assessment for PFS and at time of death for OS (Company Response to ACD, Appendix 4).[3] The results of both the basecase and exploratory MAICs for investigator-assessed PFS and OS are presented in Table 1.11.

Table 1.11: Summary of MAIC results for VenO versus zanubrutinib in previously untreated CLL

	PFS (INV)		**OS**	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Base case analyses (No COVID-19 adjustment)				
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]
Exploratory analyses for COVID-19 adjustment				
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]

	PFS (INV)		OS	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Model	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to ACD (Appendix 4, Table 16)[3]
Abbreviations: ACD = Appraisal Committee Document; CI = confidence interval; INV = investigator assessment; OS = overall survival; PFS = progression-free survival; VenO = venetoclax-obinutuzumab.

EAG Comment: Due to the width of the 95% CIs in both the basecase and exploratory MAIC models for both investigator-assessed PFS and OS, there is substantial uncertainty, [redacted]. Furthermore, as there was no common comparator arm between SEQUOIA and CLL14, the company conducted an unanchored MAIC. While the EAG agree that an unanchored MAIC is methodologically appropriate when no common comparator is present, these methods are subject to uncertainty and so the results should be interpreted with caution.

The exclusion of CIRS > 6 as a covariate raises questions regarding the validity of these results as the largest imbalance between the populations after adjusting for all covariates was the proportion of patients with a CIRS > 6. The company's rationale for excluding this covariate from the MAIC was to preserve effective sample size (ESS). However, it is unclear to the EAG why there was an inconsistency between the MAICs, as the comparion below comparing zanubrutinib with I-V, included models with and without the CIRS > 6 covariate.

In addition, this approach is inconsistent with DSU18's recommendation: "*For an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables*" (p.6).[6] There is a large imbalance between zanubrutinib (CIRS > 6 = [redacted]) and VenO (CIRS > 6 = 86.1%), and CIRS is a known predictor of outcome. Therefore, not adjusting for this covariate is likely to overestimate the effectiveness of zanubrutinib. This potentially violates an important assumption of the unanchored MAIC (i.e., that all effect modifiers and prognostic variables are adjusted for). The EAG acknowledges that the exclusion of the CIRS > 6 covariate was done to preserve ESS, as the MAIC results are very imprecise. However, the company did not report the ESS when including a covariate for CIRS > 6. Therefore, the EAG have insufficient information to judge the impact on imprecision.

The EAG believes the exploratory analyses for the COVID-19 adjustment is methodologically appropriate but also note that the result of these exploratory analyses are still uncertain due to the width of the 95% CIs in the model.

1.3.1.2 Cost-effectiveness results

The company used the results from the MAIC between SEQUOIA (pooled arm A and arm C) and CLL14 without COVID-19 adjustment as the basecase scenario in the untreated economic model, while results from the MAIC with the COVID-19 adjustment were used as a scenario analysis. The time-to-progression (TTP) for pre-progressed disease patients and mortality for pre-progressed patients (PrePS) estimates from zanubrutinib in SEQUOIA (pooled arm A and arm C) were used to model TTP and PrePS survival from VenO by adjusting the respective survival curves using the PFS hazard ratio (HR) from the MAIC and assuming constant proportional hazards.[3]

The cost-effectiveness results in the company basecase positioned zanubrutinib as the dominating intervention compared to VenO, as both deterministic and probabilistic results showed higher QALYs and less costs for the zanubrutinib arm. These results were maintained across all key scenario analyses presented by the company. The probabilitistic sensitivity analysis (PSA) results estimated the probability of each of the treatments in the untreated CLL model (zanubrutinib, acalabrutinib, ibrutinib, VenO, and I+V) being cost-effective over a range of threshold values for an additional QALY. At a £30,000 threshold for an additional QALY zanubrutinib had a [redacted] probability of being cost effective, while VenO had a probability of [redacted] of being cost-effective.

EAG comment: The EAG considers the application of PFS (including progression or death) estimates from the MAIC onto disease progression (TTP) and pre-progression mortality (PrePS) imposes strong assumptions on modelled survival, despite being a pragmatic approach under the absence of disaggregated HR estimates for TTP and PrePS. Explorations of the COVID-19 adjusted estimates as an alternative scenario was considered appropriate. The assumption of constant proportional hazards was considered strong given the relative immaturity of the trial data from SEQUOIA and the wide confidence intervals estimated in the MAIC (further critique of this assumption is provided in Sections 1.6 and 1.7).

1.3.2 Zanubrutinib versus ibrutinib plus venetoclax

1.3.2.1 MAICs

The company undertook two MAICs to assess the effectiveness of zanubrutinib compared with I-V: one against the GLOW study in older patients with and without comorbidities (Company Response to ACD, Appendix 5).[3]; and the other with the CAPTIVATE study in younger patients without comorbidities.(Company Response to ACD, Appendix 6).[3]

1.3.2.1.1 GLOW study

The company conducted a new MAIC using the GLOW study to estimate comparative efficacy between zanubrutinib and I-V in older patients with and without comorbidities (Company Response to ACD, Appendix 5).[3] Of the published papers surrounding GLOW, the company deemed Kater *et al*. (2022) to be most appropriate given it presented the most up-to-date data, with a median follow-up of 27.7 months.[8] The company used individual patient data (IPD) from the zanubrutinib arm A of SEQUOIA Cohort 1 (data cut-off 31 October 2022) and adjusted to match the characteristics of the I-V arm in GLOW.[3] However, in the company response to the ACD, Table 5, the company report that pooled arm A and arm C data were used in the MAIC in older patients with and without comorbidities.[4]

As GLOW and SEQUOIA did not contain a common comparator arm, an unanchored MAIC was conducted in accordance with the NICE DSU) guidelines and methods described by Signorovich *et al*. (2012).[6,7] As the largest imbalance between the populations after adjusting for all covariates was the proportion of patients with a CIRS > 6, the company fitted two models to both adjust and not adjust for CIRS score. Table 1.12 summarises the population characteristics for both Model 1 and Model 2 after matching by weights.

Table 1.12: Characteristics of I-V population in GLOW versus zanubrutinib population in SEQUOIA after matching

Population Characteristics		I-V (N=106)	Model 1 Zanubrutinib (ESS=152)	Model 2 Zanubrutinib (ESS=85)
IGHV mutation status	IGHV unmutated, %	67.10%	[redacted]	[redacted]
Mutation status	del17p, %	0.00%	[redacted]	[redacted]
	del11q, %	18.90%	[redacted]	[redacted]
	TP53 mutation, %	6.60%	[redacted]	[redacted]
Beta2-microglobulin	>3.5, %	69.80%	[redacted]	[redacted]
Age	Median	71	[redacted]	[redacted]
	≥ 75	33.00%	[redacted]	[redacted]
Sex	MALE, %	55.70%	[redacted]	[redacted]
Disease staging	Binet stage C, %	40.60%	[redacted]	[redacted]
	ECOG PS=0 (vs. 1-2), %	33.00%	[redacted]	[redacted]
Bulky disease	≥ 5 LDi in cm	39.00%	[redacted]	[redacted]
Time from initial diagnosis	Median	35.8	[redacted]	[redacted]
Creatinine clearance	Median	66.5	[redacted]	[redacted]
CIRS score	> 6	69.80%	[redacted]	[redacted]
Region	North America or Europe (vs. Others), %	86.80%	[redacted]	[redacted]
Cancer type	SLL, %	9.40%	[redacted]	[redacted]

Source: Company response to ACD (Appendix 5, Table 19)[3]

Footnote from Appendix 5, Table 19: Adjusted characteristics are highlighted in green and unadjusted characteristics are highlighted in pink.

Abbreviations: ACD = Appraisal Committee Document; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; IGHV = immunoglobulin heavy chain gene; IV = intravenous; I-V = ibrutinib-venetoclax; LDi = longest diameter.

The results of the MAIC for both investigator-assessed PFS and OS are presented in Table 1.13. The company noted that feedback from UK clinical experts indicated that patients were likely to relapse after completing fixed-duration therapy, whereas BTKi monotherapy could provide a continuous treatment benefit (Company Response to ACD, Appendix 5).[3] The company also noted that the clinical experts had suggested that, with longer follow-up, a separation in the Kaplan-Meier curve for PFS would become more apparent, as more patients would relapse after finishing the fixed-duration regimen (Company Response to ACD, Appendix 5).[3] As a result, the company stated that the current HR in the MAIC may be conservative (Company Response to ACD, Appendix 5).[3]

Table 1.13: Summary of MAIC results for I-V using GLOW versus zanubrutinib in previously untreated CLL

	PFS (INV)		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: Company response to ACD (Appendix 5, Table 20)[3]
Abbreviations: ACD = Appraisal Committee Document; CI = confidence interval; CLL = chronic lymphocytic leukaemia; HR = hazard ratio; INV = investigator; I-V = ibrutinib-venetoclax; OS = overall survival; PFS = progression-free survival.

EAG Comment: The company stated in their response to the ACD, Table 5, that they used pooled data from SEQUOIA (arm A and arm C).[4] However, in Appendix 5, which summaries the MAIC comparing zanubrutinib with I+V in older patients with and without comorbidities using the GLOW study, the company stated they only used data from SEQUOIA arm A.[3] The EAG is unsure as to why only data from SEQUOIA arm A was used in this comparison. The EAG consider the assumption of only using data from SEQUOIA arm A to favour zanubrutinib, as there were fewer events reported in Arm A.

Effective sample size (ESS) varied substantially between MAIC model 1 (ESS=[redacted]) and model 2 (ESS=[redacted]). Adjusting for CIRS score reduced ESS substantially but also addressed this important baseline imbalance. For both models 95% CIs were wide indicating important uncertainty in PFS and OS between zanubrutinib and I-V.

As there was no common comparator arm between SEQUOIA and GLOW, the company conducted an unanchored MAIC. The EAG agree that that this approach is methodologically appropriate but unanchored MAICs are subject to uncertainty and hence the results should be interpreted with caution.[6]

When reviewing the company response to the ACD, Appendix 5, Figures 18 and 19, there appears to be a drop in PFS after 12 months with venetoclax-based treatments.[3] However, given that I-V is a combination of venetoclax and a BTKi, the EAG cannot comment on what effect this combination has on PFS over the longer-term and whether the current HRs from the MAIC are conservative, as suggested by the company, supported by clinical expert opinion. It is also unclear to the EAG whether the company presented these data to the Delphi panel or to clinical experts as part of the 1:1 interviews. Regardless, as the EAG have not seen transcripts or summaries of the discussions held with these experts, the EAG cannot comment further on the assumptions supported by expert clinical opinion.

1.3.2.1.2 CAPTIVATE study

The company conducted a new MAIC using the CAPTIVATE study to estimate comparative efficacy between zanubrutinib and I-V in younger patients without comorbidities (Company Response to ACD, Appendix 6).[3] The company noted that, due to differences in the populations between CAPTIVATE and SEQUOIA (specifically, the average age in both studies) the ESS after matching was low. Additionally, due to the low number of OS events in SEQUOIA, the company only used investigator-assessed PFS in this MAIC (Company Response to ACD, Appendix 6).[3] Of the published papers surrounding CAPTIVATE, the company deemed Tam *et al*. (2022) and Tedeschi *et al*. (2023) to be most appropriate given they presented the most up-to-date data, with a median follow-up of 27.9 months.[9,10] As the baseline characteristics for those with and without 17p deletion were not reported

separately in CAPTIVATE, the company pooled data from Arm A of Cohort 1 and Cohort 2 (Arm C) of SEQUOIA (DCO 31 October 2022) to create a cohort that included patients with and without 17p deletion to match those in CAPTIVATE.

As CAPTIVATE and SEQUOIA did not contain a common comparator arm, an unanchored MAIC was conducted in accordance with the NICE DSU guidelines and methods described by Signorovich *et al*. (2012).[6,7] The company explored a matching model using key available covariates with either prognostic or effect-modifying potential but it was stated that this led to an insufficiently low ESS. Consequently, in order to preserve ESS the company produced a further exploratory model where only prognostic factors were adjusted for (Company Response to ACD, Appendix 6).[3] Table 1.14 summarises the population characteristics for both Model 1 and Model 2 after matching by weights.

Table 1.14: Characteristics of I-V population in CAPTIVATE versus zanubrutinib population in SEQUOIA after matching

Population Characteristics		**I-V (N=159)**	**Zanubrutinib Model 1 (ESS=51)**	**Zanubrutinib Model 2 (ESS=91)**
IGHV mutation status	IGHV mutated, %	42.6%	[redacted]	[redacted]
Mutation status	del17p (vs. del13q), %	12.7%	[redacted]	[redacted]
	del11q (vs. del13q), %	17.7%	[redacted]	[redacted]
	Trisomy 12 (vs. del13q), %	14.6%	[redacted]	[redacted]
	None (vs. del13q), %	20.9%	[redacted]	[redacted]
	TP53 mutation, %	10.3%	[redacted]	[redacted]
Sex	MALE, %	67.0%	[redacted]	[redacted]
Complex karyotype	≥3 abnormalities, %	23.3%	[redacted]	[redacted]
Disease severity	Rai stage III-IV/Binet C, %	28.0%	[redacted]	[redacted]
	ECOG PS=0 (vs. 1-2), %	69.2%	[redacted]	[redacted]
Histology	CLL, %	92.0%	[redacted]	[redacted]
Cytopenia	Haemoglobin ≤ 11, g/dL	23.3%	[redacted]	[redacted]
	Platelet count ≤ 100, 10^9 cells/L	13.2%	[redacted]	[redacted]
	Neutrophil count ≤ 1.5, 10^9/L	8.2%	[redacted]	[redacted]
Bulky disease	≥ 5 LDi in cm	30.2%	[redacted]	[redacted]
Age	AGE, Median	60	[redacted]	[redacted]
	AGE, Maximum	71	[redacted]	[redacted]
	AGE < 65, %	72.0%	[redacted]	[redacted]

Source: Company response to ACD (Appendix 6, Table 23)[3] Footnote from Appendix 6, Table 23: Adjusted characteristics are highlighted in green and unadjusted characteristics are highlighted in red. Abbreviations: ACD = Appraisal Committee Document; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; IGHV = immunoglobulin heavy chain gene; IV = intravenous; I-V = ibrutinib-venetoclax; LDi = longest diameter.	

The results of the MAIC for investigator-assessed PFS is presented in Table 1.15.

Table 1.15: Summary of MAIC results for I-V using CAPTIVATE versus zanubrutinib in previously untreated CLL

	PFS (INV)	
	Hazard ratio (95% CI)	**P-value**
Pre-matching	[redacted]	[redacted]
Model 1	[redacted]	[redacted]
Model 2	[redacted]	[redacted]
Source: Company response to ACD (Appendix 6, Table 24)[3] Abbreviations: ACD = Appraisal Committee Document; CI = confidence interval; CLL = chronic lymphocytic leukaemia; INV = investigator; I-V = ibrutinib-venetoclax; PFS = progression-free survival.		

EAG Comment: It is unclear to the EAG why the low number of events in SEQUOIA was considered an issue in the MAIC with CAPTIVATE but not in the other MAICs. The EAG acknowledges that there is uncertainty over the longer-term effectiveness of zanubrutinib due to the immaturity of SEQUOIA data (see Section 1.7) however the EAG consider that further justification was needed as to why OS was not estimated in this MAIC. The EAG do not anticipate this to have an effect on cost-effectiveness results based on how mortality is estimated in the company's untreated CLL economic model (see Section 1.6.1).

The wide 95% CI in models 1 and 2 indicates substantial uncertainty in PFS between zanubrutinib compared with I-V in younger patients without comorbidities with untreated CLL. The EAG agrees the ESS were very low for both models reflecting substantial uncertainty of the comparative efficacy of zanubruitinib and I-V in this population.

Furthermore, as there was no common comparator between CAPTIVATE and SEQUOIA, the company conducted an unanchored MAIC. Again, the EAG maintains the view that this approach, while methodologically appropriate, is subject to uncertainty and hence the results should be interpreted with caution.[6]

1.3.2.2 Cost-effectiveness results

Cost-effectiveness analyses between zanubrutinib and I-V were provided separately for older patients with and without comorbidities, and younger patients without comorbidities, based on MAIC results from GLOW and CAPTIVATE respectively. Following the proportional hazards approach for the BTKi monotherapies and VenO, the PFS HRs from model 1 of the MAIC using GLOW were applied to the TTP and PrePS curves of zanubrutinib in SEQUOIA (pooled arm A and arm C) to model TTP and

PrePS for I-V in older patients with and without comorbidities. The same approach was used to model TTP and PrePS for I-V in younger patients without comorbidities applying PFS estimates from model 2 of the MAIC using CAPTIVATE.

The cost-effectiveness results in the company basecase analysis positioned zanubrutinib as the dominant intervention compared with I-V across both populations with untreated CLL; older patients with and without comorbidities, and younger patients without comorbidities. Results were maintained across both deterministic and probabilistic analysis, where zanubrutinib showed higher QALYs and lower costs. These results were maintained across all key scenario analyses presented by the company for both populations. The PSA, comparing all treatments in older patients with and without comorbidities in the untreated CLL model, showed that zanubrutinib had a [redacted] probability of being cost effective, while I-V had a [redacted] probability of being cost-effective at a £30,000 per QALY threshold. The PSA results for the younger patients without comorbidities, comparing zanubrutinib with I+V only, showed that zanubrutinib had a [redacted] probability of being cost-effective.[4]

EAG comment: The EAG are unsure as to why the company modelled the TTP and PrePS curves for I-V in older patients with and without comorbdidies to the the zanubrutinib TTP and PrePS curves pooled from SEQUOIA arm A and arm C and not the zanubrutinib TTP and PrePS curves from SEQUOIA arm A. As discussed in Section 1.3.2.1.1, the EAG have concerns with the HRs for zanubrutinib compared with I+V in older patients with and without comorbdidies because the company only used data from SEQUOIA Arm A in the MAIC with GLOW.

The EAG note that the company, based on clinical advice, chose the least conservative models produced from both the GLOW and CAPTIVATE MAICs to inform the basecase economic models for both populations. The company explored the effect of choosing the alternative MAIC models in scenario analyses. However, as discussed in Section 1.3.2.1.1, the EAG cannot comment on what data were presented to the clinicial experts to inform this decision.

For older patients with and without comorbidities, the assessment of the MAIC in Figure 20 (Company response to ACD, Appendix 5),[3] suggests a time trend in the cumulative hazard plot and the Schoenfeld residuals, which could violate the proportional hazards assumption although, the Schoenfeld test p-values were not statistically significant across both MAIC models ([redacted]; Company response to ACD, Appendix 5)[3]

For younger patients without comorbidities, the evidence presented in Figure 26 (Company response to ACD, Appendix 6),[3] suggests a violation of the proportional hazards assumption, with Schoenfeld test p-values of [redacted] for model 1 and [redacted] for model 2 (Company response to ACD, Appendix 6).[3] The EAG considers that evidence against the use of the proportional hazards assumption across both trials further highlights the uncertainty around the long-term effectiveness of zanubrutinib compared with I-V.

"... The Company consider a comparison between CAPTIVATE and SEQUOIA to be suitable for decision making given both the EAG and the Committee deemed the SEQUOIA population to be representative of all previously untreated patients with CLL, regardless of fitness status" (p.16, Company Response to ACD).[4] The EAG would like to clarify that they did not state that the results from SEQUOIA arm A were applicable to all previously untreated CLL patients, regardless of fitness status. In the EAG report (Section 2.5), the EAG highlighted the potential uncertainty in the generalisability of SEQUOIA arm A to "unfit" untreated CLL as these patients were suitable for BR.[11]

1.4 Relapsed or refractory CLL population ACD Section 3.7, p9-10.

Additional clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus rituximab in the relapsed or refractory CLL population.

The company maintain their view that zanubrutinib would only be considered as an alternative BTKi monotherapy in the patient pathway and that fixed-duration therapies (i.e., venetoclax-based regimens) are not relevant comparators. However, to alleviate the concerns of the Committee, the company have provided evidence on the clinical and cost-effectiveness of zanubrutinib compared with VenR in the R/R CLL population.

1.4.1 Network meta-analysis

Due to time constraints, the company did not conduct additional analyses to inform the comparative efficacy of zanubrutinib and VenR but instead presented the results of Chanan-Khan *et al*. (2022), a published abstract for a NMA aligned to the DCO used in the models for zanubrutinib, ibrutinib and acalabrutinib (Company Response to ACD, Table 13).[2,4] This was a Bayesian NMA which estimated investigator-assessed PFS and OS, with the assumption of a constant hazard ratio applied in the analysis.[2] The analyses were performed using codes published by the NICE DSU and implemented with OpenBUGS.[2] The NMA contained data from the 2021 DCO from ALPINE as well as ELEVATE-RR and MURANO.[2,12,13]

The company reported that the NMA results numerically favoured zanubrutinib for investigator-assessed PFS (HR 0.69, 95% CrI 0.32 to 1.46) but that VenR was numerically favoured for OS (HR 1.27, 95% CrI 0.47 to 3.33); Company Response to ACD, Table 13.[4] The company noted that the difference between PFS and OS may be due to the MURANO study of VenR limiting prior lines of treatment to three, whereas ALPINE had no upper limit for prior treatment lines, with lines of therapy in the study ranging from one to six (Company Response to ACD, Table 13).[4] Additionally, the company acknowledge the NMA is subject to uncertainty as the network was linked by ELEVATE-RR, which only enrolled high-risk R/R CLL patients (Company Response to ACD, Table 13).[4]

EAG comment: The EAG agree with the company's statement that the evidence surrounding the efficacy of zanubrutinib compared with VenR presented in Chanan-Khan *et al*. (2022) is uncertain, as they were only able to link the network through ELEVATE-RR, which enrolled 'high-risk' R/R CLL patients only (Company Response to ACD, Table 13).[4] This uncertainty is supported by the wide 95% CrIs for both investigator-assessed PFS and OS which are sufficiently wide enough to be consistent with both benefit and harm for zanubrutinib compared with VenR .

1.4.2 Cost-effectiveness results

The company estimated the cost-effectiveness of zanubrutinib compared with VenR in R/R CLL using the existing R/R CLL partitioned survival model and the estimates from the NMA.[2,4] The company adopted the same assumptions, model settings and data sources as those for the acalabrutinib and ibrutinib comparisons in Table 10 of the company response to the ACD.[4] The only differences were in the comparative efficacy estimates and subsequent treatment modelling. It was assumed that 100% of participants would receive acalabrutinib after first-line treatment with VenR; this assumption was explored by the company in a scenario analysis (Company response to ACD, Table 13).[4]

The results were that zanubrutinib was, on average, less costly and less effective than VenR. The ICER for VenR (the more costly and more effective treatment) was £440,995. The PSA results estimated the probability of each of the treatments in the R/R CLL model (zanubrutinib, acalabrutinib, ibrutinib, and VenR) being cost-effective over a range of threshold values for an additional QALY. The PSA results showed that zanubrutinib had [redacted] probability of being cost-effective at a £30,000 threshold for an additional QALY, while VenR had a [redacted] probability. The company undertook several scenario analyses and, in all analyses, zanubrutinib was still the preferred treatment due to the high ICER associated with VenR.

EAG comment: The EAG critique of the existing R/R CLL economic model is outlined in Section 1.6 of this report. The EAG also agree with the company that there is uncertainty in the effectiveness results produced from the NMA.[4]

The EAG acknowledge that in the company's basecase and scenario analyses zanubrutinib was the preferred treatment option. However, there is considerable uncertainty in these results, particularly in the efficacy and outcome data used to inform the economic model, as illustrated by the company's PSA and scenario analyses. As outlined in Sections 1.6, 1.7 and 1.8, the EAG have concerns about the assumption of constant proportional hazards, accuracy of the survival extrapolations over the longer-term and the choice of utility values used in the economic model. The EAG were unable to explore this uncertainty in the ICERs within the time available to consider these new data.

1.5 Relapsed or refractory CLL Indirect treatment comparisons ACD Section 3.8, p10-12.

The results from the MAIC analysis used to inform the clinical effectiveness of zanubrutinib compared with acalabrutinib in both the untreated CLL and relapsed or refractory CLL populations are uncertain.

The company updated the existing MAIC comparing SEQUOIA and ELEVATE-TN (detailed in CS Section B.2.9.1) to reflect the 31 October 2022 DCO for SEQUOIA (Company Response to ACD, Appendix 3).[1,3] Data from Sharman *et al*. (2022) continued to be used for ELEVATE-TN.[14] The company state that the methodology used for the MAIC and the summary of population characteristics after matching by weights from both Model 1 and Model 2 remained unchanged from CS Section B.2.9.1.2 (Table 47).[1]

The company stated that the PFS and OS endpoints in SEQUOIA were impacted by COVID-19 deaths (with [redacted] deaths due to COVID-19 related AEs in the zanubrutinib arm), but the same impact was not seen in ELEVATE-TN as it was conducted prior to the pandemic. Therefore, the company undertook exploratory analyses in which patients who had died of confirmed COVID-19 in the SEQUOIA dataset were censored at the time of their last tumour assessment for PFS and at time of death for OS (Company Response to ACD, Appendix 3).[3] Results of both the basecase and exploratory MAICs are shown in Table 1.16.

Table 1.16: Summary of updated MAIC results for acalabrutinib versus zanubrutinib in R/R CLL

	PFS (INV)		OS	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Base case analyses (No COVID-19 adjustment)				

Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]
Exploratory analyses for COVID-19 adjustment				
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to ACD (Appendix 3, Table 12)[3]

Abbreviations: Cl = confidence interval; CLL = chronic lymphocytic leukaemia; HR = hazard ratio; INV = investigator; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival.

EAG Comment: The EAG note that, in their response to the ACD, the company stated that data for independent review committee-assessed PFS were not available for the DCO 31 October 2022.[4] Hence the updates to the MAIC made by the company used investigator-assessed PFS to ensure that the definition of PFS between SEQUOIA and ELEVATE-TN aligned (Company Response to ACD, Appendix 3).[3] The EAG considers this appropriate and unlikely to impact conclusions. The EAG note that the 95% CIs in the MAIC for both models are wide, indicating that there is uncertainty in the results.

1.6 Modelling approach ACD Section 3.11, p13-14.

1.6.1 Economic models, for both untreated CLL and relapsed or refractory CLL, built for a cost-utility analysis are more appropriate for decision making.

The company noted that, although the CS basecase presented a cost-minimisation approach, the two Excel models developed for the untreated CLL and the R/R CLL population had functionality to conduct CUAs respectively. Therefore, no further functional or structural alterations were made to the CS basecase models beyond removing the assumption of equivalent effectiveness.

EAG comment: The EAG have no concerns about the Markov structure and health states of the untreated CLL model but maintain the view that further justification for the model choice could have been provided by the company for the R/R CLL economic model.[11,15]

For the untreated model, the EAG reiterates the critique made in the EAG report (Section 4.3.6) regarding the use of PFS HR estimates (including progressions and death) to construct TTP and PrePS mortality functions, which imposes strong assumptions on TTP and PrePS despite being a pragmatic approach under the absence of effectiveness data on TTP and PrePS respectively.[1,11] Furthermore, the EAG considers that OS data obtained from the MAIC results can be meaningfully incorporated in the mortality estimated in the economic model to better represent the uncertainty of the effectiveness estimates. The impact of this may be important within a PSA given the width of the CI estimated by the MAIC.

For the comparison with ibrutinib in untreated CLL, the EAG maintains the view that data from SEQUOIA arm C should have been used in the basecase, not a scenario analysis. It is likely that the assumption to pool data from SEQUOIA arm A and arm C favoured zanubrutinib as there were fewer

progression events in arm A compared with arm C (see Table 1.1 above). The EAG also reiterate their concerns about how data from arm A and arm C were pooled (Section 4.2.6, EAG report).[11]

1.6.2 Constant relative hazards

For the untreated CLL model, the company recalls the evidence from the MAIC of zanubrutinib versus acalabrutinib in the untreated CLL population using ELEVATE-TN and the MAIC of zanubrutinib versus acalabrutinib using ELEVATE-RR and ASCEND, to conclude there is no evidence the proportional hazards (PH) assumption is violated.[1] Therefore, a proportional treatment effect is assumed across all BTKi therapies.

For the acalabrutinib arm in the untreated CLL model, the company estimated TTP and PrePS for disease-free patients using PFS estimates from the MAIC between SEQUOIA (pooled arm A and arm C) and ELEVATE-TN, updated for the 31 October 2022 data cut of SEQUOIA. The PFS HR estimates of the MAIC were subsequently applied to the modelled survival curves of TTP and PrePS from the 31 October 2022 cut of the zanubrutinib arm of SEQUOIA (pooled arm A and arm C), assuming constant relative hazards.[4]

For the ibrutinib arm in the untreated CLL model, the company applied the PFS HR estimates obtained from the 15 May 2023 data cut of ALPINE into the TTP and PrePS curves of zanubrutinib in SEQUOIA (pooled arm A and arm C) to generate the respective survival curves for ibrutinib under the constant relative hazards assumption.

The company also assumed that it was clinically resasonable to assume constant relative hazards between the BTKi treatments and provided evidence that this is a common assumption in CLL technology appraisals.[4]

EAG comment: The EAG acknowledges that the assumption of constant relative hazards is pragmatic and made under considerable uncertainty due to the immaturity of the data particularly concerning PrePS and overall survival outcomes. However, the EAG consider that this assumption could favour zanubrutinib based on the assessment of proportional hazards undertaken by the company (Company Response to ACD, Appendices 3, 4, 5 and 6).[3] Visual and statistical assessments were provided by the company for the updated MAICs informing the untreated model for the comparators acalabrutinib (Appendix 3),[3] VenO (Appendix 4)[3] and I+V (Appendix 5 and 6).[3] The visual assessment of PFS for these comparators with zanubrutinib suggests that over the longer-term there is slight convergence of the curves, which emphasises the need for longer-term data. The global Schoenfeld test was also undertaken to assess whether the proportional hazard assumption was violated. For the comparisons with acalabrutinib and VenO the proportional hazards assumption was not violated however, there was uncertainty with this for the I-V comparison. As reported in Section 1.3.2.2, evidence from the MAIC results for zanubrutinib versus I-V in untreated CLL across both populations (older patients with and without comorbidities, and younger patients without comorbidities) casts further doubt on the appropriateness of the constant proportional hazards assumption; the adoption of which could be more favourable for zanubrutinib (Company response to ACD, Appendices 5 and 6).[3]

There was no assessment of the proportional hazard assumption for the comparison of zanubrutinib with ibrutinib in R/R CLL in the original CS or in the company's response to the ACD. There was also no assessment of the proportional hazard assumption for the comparison of zanubrutinib with VenR in R/R CLL reported in the NMA results or by the company.[2]

As a result, the EAG assessed changes over time in the HRs for OS and PFS, presented in Table 1.5. The EAG note that data from ALPINE are still considered to be immature and any potential patterns observed by the EAG are subject to uncertainty.

For the R/R CLL, the company used the updated HRs for OS and PFS from ALPINE to validate their assumptions for survival extrapolations. However, when the EAG compared the HRs presented in Table 1.5 to assess the constant proportional hazards assumption there was an observed difference in the reduction in the risk of INV-assessed disease progression or death ([redacted] versus [redacted]) and OS ([redacted] versus [redacted]) for zanubrutinib when compared with ibrutinib in the two data cuts. The inclusion of the HRs from the data cut in December 2021 was conservative for OS and optimistic for PFS. The EAG acknowledge there was limited time for the company to update the economic model with these data but consider these findings should have been discussed in the company response to the ACD. The EAG consider the potential overestimation of PFS important in the R/R CLL model. As outlined in Section 1.7, all of the survival extrapolations in the R/R CLL model underestimated PFS for ibrutinib when it was compared with observed PFS in the latest DCO from ALPINE.

The EAG were unable to explore the effect of the uncertainty in the constant relative hazards assumption in the ICER results due to time constraints.

1.6.3 Safety modelling

The company acknowledge that the inclusion of AEs in the first cycle of the model is a simplification but state that the impact of AEs in the new basecase models are accounted for by calculating the impact on costs and quality of life, based on the duration of each AE.[4] Costs and disutilities are assigned according to the duration of each AE included and assessed during the first model cycle only. The company did not incorporate AEs that could occur over the time horizon of the model. Moreover, the company have updated the model to include the impact of atrial fibrillation and cardiac failure to address the concerns expressed around cardiac AEs.

EAG comment: The EAG have provided a critique on the assumption that AEs only occur in the first cycle of the model in Section 1.9. The EAG considers the quantification of the impact of cardiac AEs into costs and utilities to be a pragmatic approach to address concerns raised by the Committee. However, the EAG questions the inclusion of these AEs as part of the basecase analysis rather than a scenario analysis. The EAG consider this to be a favourable assumption for zanubrutinib especially as the rates of TEAEs included in the previous R/R CLL model were not updated to reflect the change in the profile of AEs between the arms (see Tables 1.7 and 1.8 above). AE rates for zanubrutinib in the untreated CLL model do reflect the latest DCO from SEQUOIA. However, since each comparator is informed by different trials, there are uncertainties around the definition and collection of AEs related to infections (see Section 1.1.1).

It is unclear to the EAG why the cost assigned to the AE cardiac failure in the R/R CLL model is different to the cardiac failure cost in the untreated model. The EAG did not have time to examine the uncertainty in the ICERs associated with AEs.

1.6.4 Duration of treatment effect

Across both the untreated CLL and the R/R CLL populations, patients receive first-line treatment with BTKis until death or disease progression. Therefore, the treatment effects are assumed to be maintained over the disease-free state in both models for the BTKi treatments.

EAG comment: The EAG considers this a pragmatic assumption in line with the initial CS basecase model, following the evidence available. However, the EAG has concerns about the appropriateness of applying this assumption to the I-V therapy arm, where the proportional hazards assumption may not hold for PFS survival (as noted in Sections 1.3.2 and 1.6.2). Moreover, the approach used to model mortality at post-progression was different between BTKi monotherapies and fixed-duration therapies, implying differences in treatment effects beyond progression (see Section 1.7.1.3).

1.7 Survival extrapolations ACD Section 3.12, p14-15.

Long term survival extrapolations using the most recent data is more appropriate.

1.7.1 Untreated CLL (SEQUOIA): BTKi monotherapies

The approach to model survival for zanubrutinib, acalabrutinib and ibrutinib follows the same methodology presented in the initial CS basecase economic model.[1] At progression-free (PF), patients can transition to progressed disease (PD) or death, based on TTP and PrePS data from zanubrutinib in SEQUOIA (pooled arm A and arm C), using a more recent DCO from the initial CS basecase (31 October 2022). For the comparator BTKi monotherapies, MAIC results on PFS using the latest data from SEQUOIA were applied to the TTP and PrePS survival curves of zanubrutinib (see Section 1.5 for the updated MAIC results).

1.7.1.1 TTP modelling

To model the TTP curves across the comparator interventions in the untreated CLL model, pooled data from arm A and arm C of zanubrutinib in SEQUOIA are extrapolated using the Weibull distribution to generate the zanubrutinib TTP curve. As discussed in Section 1.1.1, HRs were estimated using investigator-assessed PFS. Under the constant proportional hazards assumption, PFS relative effectiveness estimates obtained from the MAIC results are used: ELEVATE-TN model 1 MAIC for acalabrutinib; and ALPINE trial results from the latest DCO for ibrutinib.

EAG comment: The EAG maintains the view that a statistical test assessing differences on TTP between untreated 'high-risk' patients (Arm C in SEQUOIA) and untreated 'not-at-high-risk' patients (arm A) would have been more informative to determine the appropriateness of pooling data from these two subgroups together.[11]

A Weibull distribution was selected to extrapolate TTP from SEQUOIA Arm A and arm C data, based on PFS predictions (merging TTP and PrePS) matching eight-year PFS estimates from RESONATE-2. The EAG previously raised the issue that the population of RESONATE-2 may not be directly comparable to SEQUOIA and, while the Weibull model provides a good fit to the data, all distributions generally provide a good fit to the TTP and PrePS data while presenting vastly different long-term survival predictions, despite using a more recent cut of the data. Under the constant proportional hazards approach, the extrapolation function adopted was not expected to have a large impact on relative cost-effectiveness results.

Based on estimates from the initial economic model using the previous data cut, the EAG does not expect that independent review committee-assessed estimates would have a large impact on results relative to the investigator-assessed estimates used in the economic model.

1.7.1.2 PPS modelling

Following the basecase scenario in the original submission, since post-progression survival (PPS) data from SEQUOIA was deemed immature, PPS was modelled using data from the MURANO trial using an Exponential distribution (selected on statistical fit). At this stage, 100% of patients receive VenR as second-line treatment based on the MURANO trial.

EAG comment: Unlike the initial CS basecase model, which assumed equivalent clinical effectiveness, the extrapolation of post-progression survival (PPS) has an impact on the differences in effectiveness across the BTKi comparator treatments. The Exponential distribution was chosen to model PPS data from MURANO primarily on the grounds of statistical fit. However, it is possible that the predictions were too pessimistic relative to other models, which also presented a close fit to the data. The EAG considers that the extrapolation of PPS is an important uncertainty, as the Exponential distribution used might be a favourable scenario for zanubrutinib.

1.7.1.3 Untreated CLL (SEQUOIA): Fixed-duration VenO and I-V

The data source used to predict PPS for the fixed-duration therapies (VenO and I-V) were based on the ASCEND trial, which differs from the approach used for BTKi treatments, where data from the MURANO trial was used to model PPS (for zanubrutinib, acalabrutinb and ibrutinib in both the initial and the current versions of the economic model).

EAG comment: the EAG considers that not enough information was provided to justify utilising a different approach to model PPS on fixed-duration therapies than for BTKi monotherapies and the adequacy of the sources used. Moreover, little evidence was provided on the appropriate selection of the extrapolation models beyond a reference to TA689, which models PPS based on trial data from MURANO.[16] Therefore, the more pessimistic extrapolations of PPS for both VenO and I-V represent a favourable assumption for zanubrutinib.

1.7.2 R/R CLL (ALPINE)

The company undertook a later DCO from the ALPINE study and used this data to justify the choice of survival extrapolations from ALPINE in the R/R CLL economic model. The company adopted a Weibull distribution for OS and PFS in the R/R CLL model and stated that the latest ALPINE data validated these model choices.

EAG comment: The EAG compared the observed OS and PFS estimates from the ALPINE trial (mean follow up: [redacted]) to those estimated from the survival extrapolations ([redacted]) for both zanubrutinib and ibrutinib. The predicted OS for zanubrutinib and ibrutinib were more optimistic for all of the survival extrapolations than observed OS in ALPINE (zanubrutinib probability of survival at [redacted], based on observed number of events in Table 1.5 [redacted]; ibrutinib probability of survival at [redacted], based on observed number of events in Table 1.5 [redacted]). The Exponential survival extrapolation best estimated OS for both zanubrutinib (predicted probability of survival for zanubrutinib at [redacted] [redacted]) and ibrutinib (predicted probability of survival for ibrutinib at [redacted] [redacted]); Weibull had the next best prediction of OS (zanubrutinib [redacted], ibrutinib [redacted]). The company used the Gompertz and LogNormal distributions in scenario analyses. However, the EAG consider that an Exponential distribution should have been chosen for the company's basecase and the Weibull as a scenario analysis, based on the observed and predicted estimates of OS for zanubrutinib and ibrutinib.

For PFS, all survival extrapolations predicting PFS for zanubrutinib were more optimistic than observed PFS (zanubrutinib probability of being progression-free at [redacted], based on observed number of events in Table 1.5 [redacted]) except Gompertz, which was more pessimistic (zanubrutinib predicted probability of being progression-free at [redacted] [redacted]). The company used the Gompertz distribution in a scenario analysis, which the EAG considers appropriate. The Weibull extrapolation, chosen by the company for their basecase, was the closest fit ([redacted]) to observed OS in ALPINE for zanubrutinib.

All of the extrapolations underestimated PFS for ibrutinib compared to observed PFS (ibrutinib probability of being progression-free at [redacted], based on observed number of events in Table 1.5 [redacted]) in ALPINE. Both the LogNormal and Exponential extrapolations, which the company used in scenario analyses, had the same prediction of PFS at 36 months (ibrutinib predicted probability of being progression-free at [redacted] [redacted]) but had different longer-term predictions (LogNormal predictions of PFS for ibrutinib at [redacted] [redacted] and at [redacted] [redacted]; Exponential predictions of PFS for ibrutinib at [redacted] [redacted] and at [redacted] [redacted]). The Weibull distribution was the second most pessimistic extrapolation of PFS in ibrutinib. If the company were using the data from ALPINE as a validation, adjustments should have been made to the survival extrapolations chosen, especially for PFS for ibrutinib.

The comparison of the survival extrapolations with the latest DCO from ALPINE emphasises the uncertainty in the longer-term effectiveness of these treatments in R/R CLL.

The EAG did not have time to examine the uncertainty in the ICERs associated with the survival extrapolations in the untreated CLL and R/R economic models.

1.8 Source of utility values ACD Section 3.13, p15-16.

The utility values used in the company's economic models are uncertain and alternative utility values should be explored using a cost utility analysis approach.

The utility values used in the economic analyses by the company are presented in Table 1.17. The company used the utility values from their scenario analysis and the EAG basecase analysis in their basecase analysis. Scenario analyses were undertaken using different utility values, including using utility data from SEQUOIA and ALPINE, as suggested by the EAG.

Table 1.17: Utility values used for untreated CLL and R/R CLL

Analysis	PF utility	Source	PD utility	Source
Untreated CLL – basecase	0.783	TA689[16]	0.60	Holzner *et al.*[17]
Untreated CLL – scenario	0.78	TA689[16]	0.60	Holzner *et al.*[17]
Untreated CLL – scenario	0.67	TA663[18]	0.60	Holzner *et al.*[17]
Untreated CLL – scenario	0.67	GID-TA10746[19]	0.60	Holzner *et al.*[17]
R/R CLL – basecase	0.748	TA561[20]	0.60	Holzner *et al.*[17]
R/R CLL – scenario	0.78	TA689[16]	0.60	Holzner *et al.*[17]
Created by the EAG Source: Company response to ACD (Tables 2, 4, 10 and 12)[4]				

Abbreviations: ACD = Appraisal committee document; CLL = chronic lymphocytic leukaemia; EAG = Evidence Assessment Group; R/R = relapsed/refractory; PD = progressed disease; PF = progression-free.

EAG comment: The EAG has concerns about the utility values used by the company in both the untreated CLL and R/R CLL economic models. The EAG maintains the view that the searches, especially the grey literature searches, may not have captured all of relevant utility data.[11] The company provided additional evidence on utility values, previously accepted by NICE, in Table 2 in their response to technical engagement, which they used in scenario analyses.[21] It is not clear to the EAG why the company presented the results using utility values from both TA663 and GID-TA10756 when they used the same utility values for each health state.[18,19]

The EAG reiterates its concerns surrounding the utility values used in the PD health state sourced from Holzner *et al*. (2004),[17] since this study is originally based on EORTC QLQ-C30 data and the EAG found errors in the reporting of evidence from this source.[11] The EAG also noted in the EAG analyses that there was uncertainty in the cost-effectiveness results when alternative PD utility estimates were used (see EAG Report, Section 6.2.6).[11] Alternative utility values of the PD health state were not explored by the company.

The EAG appreciates that the company included an analysis using utilities from SEQUOIA and ALPINE. However, the EAG were not able to replicate these analyses in the economic models and the EAG is unsure what DCO the utilities were sourced from and, hence, cannot provide further comment.

The company also used the same utility values for the comparison of zanubrutinib with I-V in younger and "fitter" patients with untreated CLL; no justification has been provided for this assumption.

The company also maintain the assumption that the same utility values can be applied to all comparators, which might not be reflective of changes in quality of life associated with each treatment. The EAG raised this concern in the EAG report (Section 6.2.6) but overall did not consider it to be a key issue, as the treatments being evaluated were all BTKis and it could be assumed, albeit with some uncertainty, that they would have a similar effect on quality of life.[11] However, the inclusion of the venetoclax-based regimes brings further uncertainty into the analysis.

The EAG has no further comment on the utility values of AEs then those previously raised.[11]

The EAG still considers there to be considerable uncertainty in the utility estimates in both the untreated CLL and R/R CLL economic models. The effect of this uncertainty on the ICERs was not explored by the EAG due to time constraints.

1.9 Incorporating adverse events in the economic analysis ACD Section 3.14, p16-17.

Cost utility analysis including the impact of adverse events on both costs and health related quality of life for the full 30 years duration of the model time horizon would be more appropriate for decision making.

As outlined in Section 1.6.1, the company have acknowledged that assigning costs and utilities in the first cycle of the model is a simplification. However, the company have accounted for the cost and disutility associated with these AEs for the duration of the AE in an attemtpt to overcome this simplification.

EAG comment: The EAG agree with the company that this is a common assumption made in TAs but disagree with the company's statement that this is "*standard practice in economic modelling*" (p.10, Company Response to ACD).[4] The model structure and AEs should be representative of the disease and treatment pathway over the time horizon considered. The EAG considers the timing of AEs to be important, especially if they occur after one year, as these costs and disutilities are discounted. If one treatment results in AEs occurring at a later stage in the patient pathway, the current structure of the model can not account for this.

In the R/R CLL model, the EAG acknowledge there is a change in the AE profile of both zanubrutinib and ibrutinib and it is a limitation of the existing model that these changes have not been incorporated into the updated model, except for cardiac event AEs. However, given that large differences in recurring AEs have not been demonstrated across treatments in the later DCO, the approach adopted by the company, whilst simplistic, is also considered to not meaningfully affect estimates of cost-effectiveness.

1.10 Untreated CLL population that is 'high-risk' or for whom FCR or BR is unsuitable ACD Section 3.15, p17-18.

Zanubrutinib is not recommended for untreated CLL.

The company have provided additional evidence in response to the ACD.

EAG comment: The EAG have no further comments to make.

1.11 Relapsed or refractory CLL ACD Section 3.16, p18-19.

Zanubrutinib is not recommended for relapsed or refractory CLL.

The company have provided additional evidence in response to the ACD.

EAG comment: The EAG have no further comments to make.

1.12 Equality issues ACD Section 3.17, p19.

The committee considered that people with untreated CLL for whom FCR or BR is suitable to be an important subgroup. However, the committee could not make a recommendation about the clinical and cost-effectiveness of zanubrutinib for this population because the company did not present any evidence. It considered this to be an equality issue that could not be resolved in the absence of evidence for this population.

As outlined in Section 1.2, the company have not provided evidence on the effectiveness and cost-effectiveness of zanubrutinib compared with acalabrutinib in those with untreated CLL for whom FCR or BR is suitable. However, the company have provided evidence on the effectiveness and cost-effectiveness of zanubrutinib compared with I-V in "fitter" untreated CLL patients, which is summarised and critiqued in Section 1.3.2.

EAG comment: The EAG have no further comments to make.

1.13 Innovation ACD Section 3.19, p19-20.

Zanubrutinib would be considered if the company presents a cost-utility analysis.

The company have implemented this. **EAG comment**: The EAG have no further comments to make.

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