NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using acalabrutinib and venetoclax with or without obinutuzumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

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

Issue date: March 2026

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using acalabrutinib and venetoclax with or without obinutuzumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 07 April 2026
- Second evaluation committee meeting: 23 April 2026
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Acalabrutinib and venetoclax with or without obinutuzumab should not be used for untreated chronic lymphocytic leukaemia (CLL) in adults.

1.2 This recommendation is not intended to affect treatment with acalabrutinib and venetoclax with or without obinutuzumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Acalabrutinib and venetoclax with or without obinutuzumab is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether it is value for money in this population.

Why the committee made these recommendations

This appraisal only reviews the evidence for acalabrutinib and venetoclax without obinutuzumab, because the company did not include evidence for venetoclax with obinutuzumab in its analysis. The company also presented evidence for untreated non-high-risk CLL only.

Standard treatment for untreated CLL is:

- venetoclax plus ibrutinib
- venetoclax plus obinutuzumab
- acalabrutinib monotherapy, or
- zanubrutinib monotherapy.

Acalabrutinib plus venetoclax has not been directly compared in a clinical trial with standard treatments. Indirect treatment comparisons were done with venetoclax plus ibrutinib and venetoclax plus obinutuzumab. But because not all relevant comparators were included, the clinical effectiveness of acalabrutinib plus venetoclax compared to standard treatment in the NHS is uncertain.

There are also uncertainties in the company's economic model, including how subsequent treatments are modelled.

Because of these uncertainties it is not possible to determine the most likely cost-effectiveness estimates for acalabrutinib plus venetoclax. So, acalabrutinib plus venetoclax with or without obinutuzumab should not be used.

2 Information about acalabrutinib and venetoclax

Marketing authorisation indication

2.1 Acalabrutinib (Calquence, AstraZeneca) in combination with venetoclax (Venclyxto, AstraZeneca) with or without obinutuzumab is indicated for 'the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for acalabrutinib and the summary of product characteristics for venetoclax.

Price

2.3 The list price for acalabrutinib is £5,059.00 for a 60 tablet pack of 100-mg tablets. The list price of venetoclax varies depending on the pack size and dose (excluding VAT; company submission).

2.4 The company has a commercial arrangement, which would have applied if acalabrutinib and venetoclax had been recommended.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for AstraZeneca will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Chronic lymphocytic leukaemia (CLL) is a malignant disorder of the white blood cells. It is the most common type of leukaemia in England. The patient experts explained that the physical and psychological effects of CLL have a debilitating effect on their daily lives. The risk of having CLL increases with age. The condition usually progresses slowly, and symptoms develop over time. More rapid progression and a poor prognosis is commonly caused by a deletion of chromosome 17p (17p deletion) or a mutation in the gene that produces the tumour protein p53 (TP53 mutation). But 90% to 95% of people with CLL do not have the 17p deletion or TP53 mutation and so are considered to have non-high-risk CLL. The committee concluded that CLL substantially affects physical and psychological quality of life.

Clinical management

Treatment options

3.2 Usual treatment for untreated CLL includes:

- fixed-duration options, which are recommended for untreated CLL in adults (irrespective of 17p deletion or TP53 mutation status):

  - venetoclax plus ibrutinib (see NICE's technology appraisal guidance on ibrutinib with venetoclax for untreated CLL, from here referred to as TA891)
  - venetoclax plus obinutuzumab (see NICE's technology appraisal guidance on venetoclax with obinutuzumab for untreated CLL
- treat-to-progression options, which are recommended for untreated CLL in adults with a 17p deletion or TP53 mutation, or without a 17p deletion or TP53 mutation if fludarabine plus cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) is unsuitable:
  - acalabrutinib monotherapy (see NICE's technology appraisal guidance on acalabrutinib for treating CLL
  - zanubrutinib monotherapy (see NICE's technology appraisal guidance on zanubrutinib for treating CLL, from here referred to as TA931).

    The committee was aware that FCR and BR are no longer used for non-high-risk CLL. This is because targeted treatments, such as venetoclax plus ibrutinib and venetoclax plus obinutuzumab, have largely replaced chemoimmunotherapy in practice. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) stated that Blueteq data confirms that venetoclax plus ibrutinib, venetoclax plus obinutuzumab, and acalabrutinib or zanubrutinib monotherapy are commonly used in NHS practice for untreated CLL. Patient experts explained that treatment preference is shaped by individual health and social circumstances. This includes their ability to follow treatment schedules and to continue normal work and family activities. The committee was aware that the company submission did not include untreated high-risk CLL (see section 3.3). Clinical experts at the meeting commented that if recommended, acalabrutinib plus venetoclax has the potential to provide a valuable additional fixed-duration option that is taken

orally. They explained that fixed duration and treat to progression are 2 different treatment paradigms with different progressions and risks. They added that fixed-duration treatments are more intensive than treat-to-progression treatments but offer patients valuable time off treatment and may reduce the occurrence of treatment-related comorbidity. So, treatment selection needs to consider a range of clinical factors, including age, comorbidity, genetic factors and lifestyle, and be individualised to suit patient preferences and circumstances. But both fixed-duration and treat-to-progression treatments are standard first-line treatment for untreated CLL in the NHS, and all the treatment options are available to people with the condition. Patient experts at the meeting commented that people with untreated CLL tend to prefer having fixed-duration treatment. But they added that the need for regular hospital visits for obinutuzumab, which is given intravenously (with oral venetoclax), does not suit everyone. The EAG said that their clinical experts highlighted that the lower toxicity profile of acalabrutinib plus venetoclax could make it an option for older fitter patients wanting a fixed-term all-oral treatment. Clinical experts in the meeting stated there is evidence that acalabrutinib plus venetoclax may be better tolerated than venetoclax plus ibrutinib or venetoclax plus obinutuzumab. So, acalabrutinib plus venetoclax may be suitable for a broader range of people than existing fixed-duration options. The committee concluded that acalabrutinib plus venetoclax would be welcomed as a new treatment option for people with untreated non-high-risk CLL.

Company's target population

3.3 The company's submission only included people with untreated non-high-risk CLL, which is people without a 17p deletion or TP53 mutation. It also only presented evidence for acalabrutinib plus venetoclax without obinutuzumab. The committee understood that this was narrower than the

marketing authorisation (see section 2.1) and NICE's final scope on acalabrutinib and venetoclax with or without obinutuzumab for untreated CLL. The company explained that it had focused on people with untreated non-high-risk CLL because this is the population included in the AMPLIFY trial (see section 3.5). The clinical experts explained that triplet therapy including obinutuzumab was likely to be associated with greater toxicity and would potentially be used more for people with high-risk CLL.

The EAG noted that the marketing authorisation for acalabrutinib plus venetoclax applied to both high-risk and non-high-risk subgroups. It thought that considering people with untreated high-risk CLL (people who have a 17p deletion or TP53 mutation) would broaden treatment options for this subgroup. It added that the fixed-duration options currently available in the NHS were recommended for everyone with untreated CLL. But that evidence on the clinical and cost effectiveness of acalabrutinib plus venetoclax in the high-risk subgroup would be needed for this consideration. The Cancer Drugs Fund lead said that there is an unmet need in the high-risk subgroup and there may be benefit to extending the recommendation to this subgroup. The committee concluded that the company's target population of untreated non-high-risk CLL was reasonable. But it would also like to see evidence on the clinical and cost effectiveness of acalabrutinib plus venetoclax in untreated high-risk CLL.

Relevant comparators

3.4 The comparators included in the company's submission were venetoclax plus ibrutinib and venetoclax plus obinutuzumab (see section 3.8 and section 3.12). The company explained that this was because acalabrutinib plus venetoclax is a fixed-duration option and so would be used in the same population as that for which venetoclax plus ibrutinib or venetoclax plus obinutuzumab is suitable. The committee noted comments from clinical experts and the Cancer Drugs Fund lead in the meeting about

current standard care in the NHS (see section 3.2). It concluded that both fixed-duration and treat-to-progression treatments are relevant comparators for this appraisal.

Clinical effectiveness

Data sources

3.5 AMPLIFY is an ongoing, open-label, phase 3, randomised controlled trial comparing acalabrutinib plus venetoclax (n=291) with FCR or BR (n=290). The primary outcome measure was progression-free survival (PFS), assessed by an independent review committee (IRC). The company presented results from the interim analysis of the trial (April 2024 data cut) with a median follow up of 40.8 months. The trial included people aged 18 and over with untreated CLL without a 17p deletion or TP53 mutation. People in the trial had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and chemoimmunotherapy was considered suitable for them.

ASCEND was an open-label, phase 3, randomised controlled study comparing acalabrutinib monotherapy with investigator's choice (idelalisib plus rituximab or BR) in people with relapsed or refractory disease. The primary endpoint was PFS, assessed by an IRC in the intention-to-treat population. People had a median of 2 prior lines of treatment. The interim analysis was done at a median follow up of 16.1 months. The company used overall-survival data from the intervention arm of the trial to inform post-progression survival data in the model because the post-progression survival data in AMPLIFY was immature.

Generalisability

3.6 The committee noted that the control arm in the company's pivotal trial AMPLIFY was chemoimmunotherapy but this is no longer standard treatment for untreated CLL in the NHS. Clinical experts in the meeting

commented that while the trial population was reasonably generalisable to clinical practice, older frailer people with multisystem comorbidity were excluded from the trial because chemoimmunotherapy would not be suitable for them. People in the trial had a mean age of 59.9 years at baseline and this was used as the starting age in the company's model (see section 3.11). The EAG explained that its clinical experts had suggested the mean age at treatment for untreated CLL in the UK was in the 70s. It noted this was in line with data from real-world evidence studies in Europe where the median age at diagnosis of CLL was around 70 years. So, the EAG preferred to adjust the model starting age to 71 years to be consistent with the modelling in TA891. The committee noted NHS real-world evidence from the Systemic Anti-Cancer Therapy (SACT) database. In people with untreated CLL, the mean starting age for venetoclax with ibrutinib was between 64 and 65 years (n=1,025). For venetoclax plus obinutuzumab it was between 62 and 66 years (n=108). Clinical experts in the meeting commented that the SACT data was collected over a timeframe that included the COVID-19 pandemic and this may have reduced the average age of patients treated during this time. The committee noted comments from the EAG that the SACT data would be a reasonable lower-bound estimate for the mean age in the model. The committee concluded it was satisfied that the AMPLIFY trial was largely generalisable to the population who would have acalabrutinib plus venetoclax in NHS practice. But it noted that the average age in the trial would be younger than what would be seen in clinical practice and that this introduced uncertainty. The committee considered that the EAG's starting age in the model was more appropriate for decision making.

Trial results

3.7 Evidence from AMPLIFY showed that, at the median 40.8 months follow up, acalabrutinib plus venetoclax was associated with:

- improved IRC-assessed PFS (hazard ratio 0.65; 95% confidence interval [CI] 0.49 to 0.87; p= 0.004)
- an improved overall-survival hazard ratio of 0.33 (95% CI 0.18 to 0.56, p<0.001).

Evidence also showed that the improvement in PFS was sustained at month 24 (the company considered the data confidential so it cannot be reported here) and month 36 (76.5% in acalabrutinib plus venetoclax versus 66.5% in FCR or BR). The committee concluded that evidence showed that acalabrutinib plus venetoclax improved PFS and overall survival compared with FCR or BR, but that the longer-term treatment effect is uncertain because of the relatively short follow-up duration of the trial.

Indirect treatment comparisons

ITCs done by the company

3.8 There were no head-to-head comparisons of acalabrutinib plus venetoclax with the comparators the company included in its submission, which were venetoclax plus ibrutinib, and venetoclax plus obinutuzumab. So, after exploring the feasibility of various of approaches the company did indirect treatment comparisons (ITCs). The company presented the following analyses:

- An unanchored simulated treatment comparison (STC), which the company considered to be the most suitable for comparing acalabrutinib plus venetoclax with venetoclax plus ibrutinib and venetoclax plus obinutuzumab. This analysis was based on data from 4 trials:
  - AMPLIFY (acalabrutinib plus venetoclax)
  - GLOW and CAPTIVATE FD (venetoclax plus ibrutinib)
  - CLL14 (venetoclax plus obinutuzumab).

- A Bucher ITC to compare acalabrutinib plus venetoclax with venetoclax plus obinutuzumab using data from AMPLIFY and CLL13 (using FCR or BR as a common comparator).

  The company considered the results of these analyses to be confidential and so they cannot be reported.

  Both the company and the EAG noted the heterogeneities across the trials included in the ITCs. The EAG said that baseline characteristics such as age and ECOG scores varied across trials. It also noted that follow-up durations and assessment methods (investigator-assessed versus IRC-assessed) in trials also differed. It also highlighted that among the trials included in the analyses, only AMPLIFY and CLL13 excluded patients with a 17p deletion or TP53 mutation, while CAPTIVATE FD and CLL14didn't specify such restrictions for recruitment.

  The company estimated restricted mean survival time (RMST) in both the unanchored STC and Bucher ITC, rather than hazard ratios. The company explained that proportional hazards assumptions were not met in the STC, so it did not estimate hazard ratios.

EAG's critique of the ITCs presented by the company

3.9 The EAG noted that the company's ITCs were limited to the comparisons between acalabrutinib plus venetoclax and fixed-duration treatments, and did not include all potentially relevant comparators. Regarding the company's choice of estimated RMST, the EAG noted that the assumption of proportional hazards assessments is often subjective, and presenting hazard ratios would benefit decision making.

Regarding the company's unanchored STCs, the EAG stated that unanchored STCs are among the least robust form of ITC. This is

because STCs rely entirely on the assumption that all relevant treatment-effect modifiers are observed and adjusted for in the analysis. This, as warned about in NICE Decision Support Unit technical support document 18, is rarely met in practice, particularly in oncology where unmeasured confounding is common. The EAG noticed that not all relevant prognostic factors, such as 13q deletion mutation status and complex karyotypes, were adjusted for in the STC. It also noted that each of the comparator trials included in the STC included people with a TP53 mutation or a 17p deletion, a known prognostic factor in CLL. But AMPLIFY did not include people with a TP53 mutation or a 17p deletion, so this mutation status could not be adjusted for in the analysis. The EAG said that the analysis not including all relevant prognostic factors, and the lack of adjustment for TP53 mutation or 17p deletion across trials, was likely to overestimate the treatment effect of acalabrutinib plus venetoclax.

Regarding the company's Bucher ITC, the EAG noted that AMPLIFY and CLL13 appear to have similar baseline characteristics. But it said that the proportions of people with an ECOG performance score of 0 and having FCR or BR were higher in CLL13, suggesting a fitter population. The EAG thought that the treatment effect of acalabrutinib plus venetoclax compared to venetoclax plus obinutuzumab was also likely to be overestimated in the company's Bucher ITC.

Committee discussion on ITCs

3.10 The committee questioned why other types of ITCs, such as network meta-analyses (NMAs) and multi-level network regression (ML-NMR), which the EAG considered more appropriate and feasible and which were requested at clarification, had not been provided. The company explained that it did not do an NMA because this would not allow the comparison of some established treatment-effect modifiers across trials, mainly immunoglobulin heavy chain variable (IGHV) region expression and 11q deletion mutation. The committee questioned how treatment-effect

modifiers had been tested. The company explained that these were explored by subgroup analyses and then validated with opinions from company clinical experts. A clinical expert at the meeting explained that it is uncertain whether 11q deletion mutation is a treatment-effect modifier. They said that IGHV region mutation status may be a more relevant treatment-effect modifier for chemoimmunotherapy treatments than the targeted treatments included in the NMAs.

The EAG said that the company's reasons for not doing an NMA were the very reasons why an ML-NMR would have been the more appropriate approach. It noted that the biases in the company's ITCs were not only caused by differences in baseline characteristics but were compounded by using RMST instead of hazard ratios. The EAG explained that hazard ratios are independent of the baseline characteristics and risk. In contrast, RMST is sensitive to the underlying hazard rate and so needs a wider range of prognostic factors and treatment-effect modifiers to be controlled for in the analysis. The company stated that its assessment of treatment-effect modifier was done on the hazard-ratio scale, but the EAG considered this inappropriate when the analysis itself was done using RMST. The company also indicated that the only way to identify treatment-effect modifiers was through subgroup hazard ratios and that doing an ML-NMR would need CAPTIVATE FD to be removed from the analysis because it is a single-arm study. The EAG did not agree that subgroup hazard ratios were the only appropriate method for identifying treatment-effect modifiers.

The committee was aware that the company's ITCs did not include all potentially relevant comparators (see section 3.9) and so were likely incomplete. It noted the heterogeneity across trials included in the company's ITCs and the inconsistent reporting of covariates across trials. The committee also noted the uncertainties in the company's chosen STC and the Bucher ITC. In particular, it highlighted that the STC needs all

relevant treatment-effect modifiers to be observed and adjusted for, an assumption that was not supported by the available evidence. In addition, it also noted the uncertainties in potentially relevant prognostic factors in untreated CLL, and potential treatment-effect modifiers for different types of treatments for untreated CLL in clinical trials such as chemoimmunotherapy and targeted treatments. It also acknowledged the EAG's concern that the company had not presented a clear assessment of the potential covariates or testing of potential treatment-effect modifiers.

The committee concluded that the company's ITCs did not include all relevant comparators and so were not acceptable for decision making. It noted the substantial uncertainties and lack of evidence to support the assumptions underlying the company's STC. Given the incomplete ITCs presented so far, and the associated uncertainties, it requested that the company provide:

- Systematic literature reviews identifying all relevant studies comparing the treatment effect of acalabrutinib plus venetoclax with all other relevant comparators (see section 3.4).
- Feasibility assessments demonstrating the appropriateness of its preferred ITCs in comparison with other potentially feasible approaches.
- NMAs estimating hazard ratios for the outcome of PFS, overall survival, and time to disease progression, assessing the proportional hazards assumption and using appropriate alternative models where this assumption is not met.
- A clear assessment of the potential covariates and potential treatment-effect modifiers that may have an impact on the treatment effect of acalabrutinib plus venetoclax compared with other treatments included in the ITCs. These include but are not limited to age, fitness, ECOG status, IGHV status, 11q deletion mutation status, and follow-up duration. For each of the treatment-effect modifier assessments, the

committee asked the company to provide clear information on whether the interaction analysis was adjusted for other covariates or stratification factors.

- Clarification of the handling of the 17p deletion or TP53 mutation status in relevant trials.

Economic model

Company's modelling approach

3.11 The company submitted a semi-Markov model with 3 health states: progression-free, progressed disease, and death. There were additional on- or off- treatment sub-states within progression-free and progressed-disease health states. The model had a lifetime time horizon of 40 years and a 28-day cycle length. Everyone entered the model in the progression-free on-treatment health state. The transition probabilities for progression-free to progressed disease and progression-free to death were informed by the AMPLIFY trial. Because of the immaturity of the AMPLIFY post-progression data, the transition probabilities for progressed disease to death were informed by the ASCEND trial. The EAG considered the model structure appropriate for modelling untreated non-high-risk CLL. But it noted that the model did not include all relevant comparators (see section 3.4). The committee concluded that the company's model structure was acceptable for decision making, but it would like the company to revise the model by including all relevant comparators in the model.

Equal-efficacy assumption

3.12 Given the uncertainties in the unanchored STC and the Bucher ITC, the company assumed equal efficacy between acalabrutinib plus venetoclax, venetoclax plus ibrutinib and venetoclax plus obinutuzumab, in the outcomes of:

- time to progression (TTP)

- PFS
- post-progression survival (post-PS).

So, the same survival curve was used for acalabrutinib plus venetoclax and the comparators in the model. To provide further evidence for the equal-efficacy assumption and to validate the ITC outcomes the company also did a modified Delphi panel with UK clinical experts. This panel reached a consensus that acalabrutinib plus venetoclax is a suitable alternative to venetoclax plus ibrutinib and venetoclax plus obinutuzumab for PFS, overall survival and resource use. The panel also reached consensus that acalabrutinib plus venetoclax has a more favourable safety profile than venetoclax plus ibrutinib and a comparable safety profile to venetoclax plus obinutuzumab. It also reached consensus that health-related quality of life was similar between acalabrutinib plus venetoclax and venetoclax plus ibrutinib. But the panel did not reach a consensus on whether all treatments have equivalent time to next treatment. Nor did it reach a consensus on whether health-related quality of life is equivalent between acalabrutinib plus venetoclax and venetoclax plus obinutuzumab.

The EAG's clinical experts questioned the validity of the assumption of equivalent efficacy and considered venetoclax plus ibrutinib may be more effective than acalabrutinib plus venetoclax. Experts noted that acalabrutinib plus venetoclax has an improved cardiovascular safety profile compared with venetoclax plus ibrutinib. But it considered that this advantage is limited because the adverse events are generally manageable within the NHS. The EAG also identified an unanchored matching-adjusted indirect comparison (MAIC; Munir et al. 2025) which suggested venetoclax plus ibrutinib had superior PFS and undetectable minimal residual disease (from pooled CAPTIVATE FD and GLOW data) compared with acalabrutinib plus venetoclax. The EAG also questioned the representativeness of the Delphi panel and the value of

its findings in informing comparative effectiveness across treatments. For example, only 35% (33 out of 95) of the invited experts took part in the panel. Additionally, the panel's response rate declined from 67% (22 out of 33) from round 1 to 48% (16 out of 33) to round 2. And the panel did not elicit quantitative estimates for survival differences. The EAG was not satisfied with the equivalence assumption but maintained it in its base case because the company did not provide any of the alternative indirect comparisons the EAG had requested.

A clinical expert explained that a recent study suggested that venetoclax plus ibrutinib and venetoclax plus obinutuzumab may have equal efficacy. But they said that it would be challenging to assume equal efficacy for PFS and overall survival across treatments, given the relatively short follow-up duration of AMPLIFY. Median PFS had not been reached in AMPLIFY. The clinical expert said that it is too early to make an assumption for PFS based on AMPLIFY data because the trial does not provide any data on time to next treatment. The clinical expert explained that it is possible to assume equal efficacy between venetoclax plus obinutuzumab and venetoclax plus ibrutinib based on the recent CLL17 trial (Al-Sawaf et al. 2025). The committee recalled its discussions on the company's ITCs (see section 3.10). Because the company's ITCs (both the unanchored STC and the Bucher ITC) were incomplete and uncertain, it was not possible to assume equal efficacy without further evidence and analysis. So, it concluded that it is not appropriate to assume equal efficacy of acalabrutinib plus venetoclax, venetoclax plus ibrutinib and venetoclax plus obinutuzumab.

Treatment duration

3.13 The company derived time on treatment for acalabrutinib plus venetoclax (14 cycles for acalabrutinib and 12 cycles for venetoclax) using time to treatment discontinuation (TTD) Kaplan–Meier data directly from AMPLIFY without extrapolation. There was no TTD Kaplan–Meier data for

venetoclax plus obinutuzumab or venetoclax plus ibrutinib from clinical trials, so the company assumed equivalent TTD to acalabrutinib plus venetoclax. For venetoclax plus ibrutinib, the company extended the Kaplan–Meier curve to 15 total cycles to reflect trial protocol differences. The EAG considered that assumption of TTD equivalence across all regimens was not sufficiently supported and was inconsistent with available evidence. The EAG stated that published trial data and clinical experience indicates that the discontinuation patterns differ between acalabrutinib plus venetoclax, venetoclax plus ibrutinib and venetoclax plus obinutuzumab. Clinical opinion to the EAG was that treatment discontinuation is mainly driven by adverse events and that a less toxic regimen such as acalabrutinib plus venetoclax would be expected to have higher completion rates. Higher completion rates translate into longer time on treatment, and so longer time to treatment discontinuation. In the EAG base case, a linear decline in TTD was applied for acalabrutinib plus venetoclax from cycle 1 to align with observed trial completion. For venetoclax plus ibrutinib, the EAG used the average TTD estimates from GLOW and CAPTIVATE FD. For venetoclax plus obinutuzumab, the EAG applied the average TTD from CLL14 and CLL13.

The committee highlighted that trial data showed different discontinuation patterns compared to clinical practice. Clinical experts stated that it was difficult to determine the exact discontinuation rates because of the lack of direct comparisons. They also stated that in their experience, venetoclax plus obinutuzumab is delivered in full most of the time. They added that venetoclax plus ibrutinib use in the UK varies because of the cardiovascular-related risk and that there is more discontinuation with this treatment. Clinical experts also highlighted that discontinuation rates in a clinical trial may be higher than in the NHS. They said that this is because trial rules may require treatment discontinuation for safety reasons in situations where, in clinical practice, the dose would more likely be adjusted rather than completely discontinued. The committee decided that

there was uncertainty in the company's assumption that all treatments in the model have equivalent time on treatment.

The EAG noted that the company applied the same Kaplan–Meier curve for TTD to acalabrutinib plus venetoclax, venetoclax plus ibrutinib and venetoclax plus obinutuzumab, with the probability of remaining on treatment declining over time. It explained that using a single curve implied that shorter fixed-duration regimens, such as venetoclax plus obinutuzumab, achieve a higher overall completion rate than acalabrutinib plus venetoclax. They said that this in turn increases estimated treatment costs for venetoclax plus obinutuzumab relative to acalabrutinib plus venetoclax. The EAG noted that although the curve shape is the same across regimens, the resulting completion rates differ because of the different treatment durations. The company stated that it accounted for regimen-specific cycle lengths and durations and that only the TTD curve itself was assumed to be shared because of limited data. The EAG used the TTD curve for acalabrutinib plus venetoclax only. It derived discontinuation rates for venetoclax plus ibrutinib (the average of GLOW and CAPTIVATE FD) and venetoclax plus obinutuzumab (the average of CLL14 and CLL13) from their respective trials. The committee concluded that it preferred the EAG's approach for deriving time on treatment, which was based on TTD from the corresponding trial data for each treatment. But it noted that not all relevant comparators are included in the company's modelling (see section 3.9).

Relative dose intensity

3.14 The company took relative dose intensity (RDI) for acalabrutinib plus venetoclax directly from AMPLIFY. The company considers the values to be confidential so they cannot be reported here. For venetoclax plus ibrutinib and venetoclax plus obinutuzumab, the company assumed 100%RDI because trial-based or publicly available data for these regimens was not available. The company explained that its approach

was consistent with TA891 (venetoclax plus ibrutinib). The EAG did not consider it appropriate to assume 100% RDI for venetoclax plus ibrutinib and venetoclax plus obinutuzumab while applying a lower RDI for acalabrutinib plus venetoclax. The EAG also explained that assuming 100% RDI for venetoclax plus ibrutinib and venetoclax plus obinutuzumab was likely to overestimate treatment use for these comparators and introduce a cost bias in favour of acalabrutinib plus venetoclax. Clinical evidence and EAG expert opinion suggested that toxicity with venetoclax plus ibrutinib and venetoclax plus obinutuzumab is at least comparable to, and may be greater than, with acalabrutinib plus venetoclax. So 100%RDI for venetoclax plus ibrutinib and venetoclax plus obinutuzumab is unlikely and a lower RDI for these regimens compared with acalabrutinib plus venetoclax is more plausible. The EAG base case applied 100% RDI for all treatments. It stated that maintaining a consistent RDI across treatment arms better reflects real-world practice and avoids introducing bias into relative cost comparisons. It also explored scenarios that applied consistent RDI for venetoclax across all arms and aligned the RDI for ibrutinib and obinutuzumab with the same value used for acalabrutinib in AMPLIFY. The committee considered the company's RDI assumptions, with lower values for acalabrutinib plus venetoclax than the comparators, to be implausible. It concluded that it preferred the EAG's approach of applying a consistent RDI (100%) across treatments included in the company's analysis so far. But it noted that not all relevant comparators are included in the company's modelling (see section 3.9).

Utility values

Source of utility values

3.15 The company mapped the EQ-5D-5L values from AMPLIFY to EQ-5D-3L to estimate the utility value for the progression-free on-treatment (oral treatment) health state. The same utility value was applied to the progression-free off-treatment health state (the company considers the

exact values to be confidential so they cannot be reported). The same utility value was applied for progression-free off-treatment. The company explained that there was limited post-progression data from AMPLIFY. So, it applied decrements from Kosmas et al. (2015) to the progression-free utility value for progressed-disease, on- and off-treatment. It also applied decrements for intravenous treatment and adverse events. The EAG was satisfied with the overall methods used in the company's approach. But it noted that the progression-free on-treatment (oral treatment) utility value, used as the starting point for the company's approach, was higher than the UK-population age-matched utility. So, the company's approach may overestimate quality of life for people with CLL. The EAG also suggested that the assumption of equal progression-free utilities for on-treatment (oral treatment) - and off-treatment states was implausible. It said that this is because it would expect being off treatment to be associated with an improved quality of life once treatment-related toxicity resolves. It further noted concerns related to the risk of bias when relying on trial values as the main source of utility estimates. It said that this is because improvements in utility early in treatment may be transient and may not represent stable health states over time. So, the EAG preferred to use utility values directly from Kosmas et al., which included an improvement in progression-free utility for the off-treatment compared with on-treatment health state. Clinical experts at the meeting explained that the quality of life of people with CLL is expected to be lower than in the UK general population. The committee noted that in the EAG's preferred values, the improvement in progression-free utility was large (greater than 0.1) when moving from on treatment to off treatment. Patient experts commented that not everyone reports difficult side effects on treatment and that this varies by treatment. They noted that being off treatment can bring additional anxiety and worry about CLL not being actively managed. Clinical experts commented that an improvement in quality of life would usually be expected off treatment compared with on treatment, but this is not absolute and there is individual variability. The committee noted that

the EAG had presented a scenario based on the company's approach using values from the AMPLIFY trial (with relative decrements from Kosmas et al.) but capping trial values at general-population utility values for age. It decided that this was its preferred approach to use in the modelling. The committee concluded that it preferred to use the EAG scenario of AMPLIFY-derived utility values capped at general-population utility values for age. It also requested that the company provide further justification for its assumption that progression-free utility value was the same on treatment (oral treatment) and off treatment.

Modelling of subsequent treatments

3.16 The company assumed that everyone whose disease progressed on acalabrutinib plus venetoclax, venetoclax plus ibrutinib or venetoclax plus obinutuzumab had subsequent treatment. So it applied a subsequent-treatment cost to all progressed-disease health states. It explained that this decision was based on clinical-expert opinion and previous technology appraisals. Clinical advice to the EAG was that not everyone will go on to have further treatment. So, the EAG preferred to use midpoint estimates that were between trial-reported subsequent-treatment rates and the disease-progression rates of each arm to derive the overall proportion of people having subsequent treatment. Clinical experts at the meeting explained that estimating the proportion of people who will have subsequent treatment is difficult because it depends on factors such as age at the time of progression, comorbidities and overall life expectancy. While it was expected that most people would have subsequent treatments, the clinical expert advised that the actual proportion would be less than 100%. They noted for example, that people with a mutated IGHV region (a favourable-risk group) may remain in remission for many years after fixed-duration treatment and may never need further treatment. This makes it hard to quantify future treatment needs for people with non-high-risk CLL. The clinical expert added that most people will eventually need subsequent treatment, but whether they actually have

it will depend on their age, comorbidities and overall life expectancy at the time of progression. They said that people may remain well for many years after initial treatment. They explained that when their disease eventually progresses, they may no longer be eligible for subsequent treatment because of changes in health status or comorbidities linked to older age. The clinical expert explained that because trials have limited follow up, they do not fully capture this effect, making it difficult to estimate the true proportion of people who will have further treatment. The clinical expert agreed that the EAG's use of midpoint estimates for deriving the proportion of subsequent treatments was a reasonable approach. The company argued that applying a lower proportion would be inconsistent with post-progression overall-survival estimates based on ASCEND. The trial assessed the treatment effect of acalabrutinib monotherapy on IRC-assessed PFS and overall survival in adults with relapsed or refractory CLL (see section 3.5).

The company derived subsequent-treatment distributions from UK clinical-expert estimates. It assumed that real-world use would exceed that seen in the trial datasets because of trial immaturity. It also assumed that the sequence of subsequent treatments does not affect post-progression survival. This approach resulted in a large proportion of people being assigned to acalabrutinib or zanubrutinib monotherapy and venetoclax-based regimens, with smaller proportions having ibrutinib or venetoclax monotherapy. The EAG considered that the company's assumed proportion of subsequent treatments did not align with the evidence from AMPLIFY. The EAG's clinical experts agreed that the company's estimates for the proportion of people having acalabrutinib, ibrutinib, venetoclax or zanubrutinib monotherapies or venetoclax plus rituximab as subsequent treatment appeared too high. But they advised that the trial-based estimates were likely too low because of the limited follow up. The EAG's clinical experts noted that ibrutinib initiation is now uncommon in UK clinical practice and so should be assigned to only a

small proportion of people. They advised that acalabrutinib remains the most frequently used second-generation Bruton's tyrosine kinase (BTK) inhibitor, with zanubrutinib use expected to increase but not exceed acalabrutinib. They also considered the company's estimate of venetoclax monotherapy use to be too high, noting that venetoclax plus rituximab is generally preferred, with venetoclax monotherapy reserved for frailer patients. On this basis, the EAG thought that the company's distribution underrepresents venetoclax plus rituximab and overrepresents monotherapies, which leads to subsequent treatment costs being underestimated. For the distribution of subsequent treatments, the EAG applied revised proportions informed by feedback from its clinical advisers.

The Cancer Drugs Fund lead outlined recent prescribing trends, noting that patterns are influenced by the timing of NICE positive guidance publication, including:

- venetoclax plus rituximab in 2019 (see NICE's technology appraisal guidance on venetoclax with rituximab for previously treated CLL)
- zanubrutinib in 2023 (see TA931).

The Cancer Drugs Fund lead explained that venetoclax plus rituximab use is declining, while acalabrutinib and zanubrutinib are now each used for around a third of patients. They said that this means that approximately three-quarters of patients have 1 of these 2 BTK inhibitors and the remaining quarter has venetoclax plus rituximab. The committee considered that the EAG's estimates broadly reflect current practice, although they should include slightly lower use of venetoclax plus rituximab, consistent with its ongoing decline. The clinical expert explained that, if recommended, fixed-duration acalabrutinib plus venetoclax would change the pattern of retreatment. In current pathways people who have initial treatment with a BTK inhibitor such

as acalabrutinib would not usually go on to have retreatment with acalabrutinib at progression. But evidence suggests that people who have initial treatment with fixed-duration acalabrutinib plus venetoclax could still have retreatment with BTK inhibitors or venetoclax at relapse. This means that future retreatment options if acalabrutinib plus venetoclax was available would differ from the current treatment landscape. The clinical expert noted that introducing acalabrutinib plus venetoclax into the pathway effectively adds an additional line of treatment. For example, in current practice, someone who had venetoclax plus obinutuzumab and whose condition later relapses may have treat-to-progression acalabrutinib or zanubrutinib, after which options are limited. In contrast, if fixed-duration acalabrutinib plus venetoclax is used at first line then venetoclax plus rituximab remains available later, along with time-to-progression treatments. The committee noted that including acalabrutinib plus venetoclax in the pathway could create the potential for up to 3 lines of treatment if people have acalabrutinib plus venetoclax at first line.

The committee considered that the EAG's estimates for the proportions and distribution of subsequent treatment may more closely reflect real-world practice. But because not all relevant comparators were included, it did not consider the company's modelling of subsequent treatment to be appropriate. The committee could not make any conclusions on the proportion or distribution of subsequent treatments.

The committee noted that, if acalabrutinib plus venetoclax is recommended, the choice and sequence of subsequent treatment for people who have had it may differ from some of those who have had other treatments at first line. The committee also considered that it is inappropriate to model costs associated with subsequent treatments without also modelling treatment benefits. Given the potential for acalabrutinib and zanubrutinib to introduce an additional line of

subsequent treatment for some people, the committee requested that the company:

- Update the modelling of subsequent treatments to reflect the changes to the treatment pathway if acalabrutinib plus venetoclax is introduced. This needs to include all relevant comparators and incorporate both the costs and benefits associated with subsequent treatments.
- Provide evidence and information on subsequent-treatment selection, the proportion of people having subsequent treatment following progression, and the distribution of subsequent treatments, for each arm.
- Do sensitivity analyses exploring the uncertainty in the subsequent-treatment pathway.

Cost-effectiveness estimates

No plausible ICERs

3.17 The committee restated that the company's ITCs and economic model did not include all relevant comparators (see section 3.10) and that it would like these to be included. The committee noted the substantial uncertainty and issues in the evidence and modelling, particularly:

- that the longer-term treatment effect of acalabrutinib plus venetoclax is uncertain (see section 3.7)
- that not all relevant comparators are included in the company's submission (see section 3.4)
- that the treatment effect of acalabrutinib plus venetoclax relevant to current standard care for untreated CLL is unknown (see section 3.10)
- the company's equal-efficacy assumption for acalabrutinib plus venetoclax, venetoclax plus ibrutinib and venetoclax plus obinutuzumab is not appropriate (see section 3.12)

- the company's assumption of equivalent time on treatment for venetoclax plus obinutuzumab and venetoclax plus ibrutinib to that of acalabrutinib plus venetoclax (see section 3.13)
- the company's approach of assuming 100% RDI for venetoclax plus ibrutinib and venetoclax plus obinutuzumab while applying a lower RDI to acalabrutinib plus venetoclax (see section 3.14)
- that the company's assumption of progression-free utility is the same on treatment (oral treatment) and off treatment (see section 3.15)
- the company's assumption that all patients in the progressed-disease health state have subsequent treatment (see section 3.16)
- the company's modelling of subsequent treatment (see section 3.16).

Considering the uncertainties and because some comparators are not included in the company's ITCs or in the model, the committee concluded that it could not arrive at a plausible range of incremental cost-effectiveness ratios (ICERs) or scenarios on which to base a decision.

Committee's preferred assumptions

3.18 The committee concluded that the cost-effectiveness modelling for acalabrutinib plus venetoclax was uncertain (see section 3.17). But it said that the company's overall model structure was acceptable for decision making (see section 3.11). It determined some preferred assumptions based on the current modelling, which were to use the EAG's:

- model starting age (71 years), which was consistent with TA891 (see section 3.6)
- approach for deriving time on treatment, which was based on TTD for each treatment on its corresponding trial data; but the committee was aware that no relevant comparators were included in the model (see section 3.13)

- approach of applying a consistent RDI (100%) across treatments; but the committee was aware that no relevant comparators were included in the model (see section 3.14)
- scenario on utility values, which used the company's approach for calculating the values but capped them at general-population utility values for age (see section 3.15).

Requested information and additional analyses

3.19 The committee requested the company to:

- provide evidence on the clinical and cost effectiveness of acalabrutinib plus venetoclax in untreated high-risk CLL (see section 3.3)
- include all relevant comparators in the clinical evidence and economic model (see section 3.4)
- provide updated systematic literature reviews including all relevant comparators, feasibility assessments of ITC or NMA methods, and full NMAs including all relevant comparators for PFS, overall survival and TTD, with:
  - a clear assessment of covariates and treatment-effect modifiers (for example, age, ECOG score, and IGHV region and 11q deletion mutation status)
  - clear reporting of covariates or stratification adjustments or both
  - clarification on how TP53-normal status was handled across trials (see sections 3.9 and 3.10).
- provide updated modelling of subsequent treatments that reflects the potential pathway changes introduced by acalabrutinib plus venetoclax, incorporating costs and benefits (see section 3.16)
- provide supporting evidence on subsequent-treatment selection, progression proportions, and treatment sequence for each arm (see section 3.16)
- do sensitivity analyses to explore uncertainty in downstream treatment pathways (see section 3.16)

- provide further justification for the assumption that the progression-free utility value was the same in the on-treatment (oral treatment) and off-treatment health states (see section 3.15).

Managed access

Recommendation with managed access

3.20 Having concluded that acalabrutinib plus venetoclax could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period. The committee was aware that the company had provided a managed access proposal. This proposal included longer-term data collection from AMPLIFY and the possibility of further data on comparators from SACT data. It noted that there were substantial uncertainties in the evidence and modelling and no plausible ICERs on which to base its decision. So, it had requested the company perform additional analyses and provide further information. The committee concluded that it could not make a conclusion on whether to recommend acalabrutinib plus venetoclax for use with managed access.

Other factors

Equality

3.21 The committee considered submissions from clinical experts noting that NHS infrastructure varies between tertiary centres and district general hospitals. The committee heard that smaller hospitals may lack the monitoring capacity or day-unit space needed for obinutuzumab infusions and tumour lysis syndrome monitoring, creating potential inequalities in access to some current treatments. In contrast, outpatient BTK inhibitor treatments such as acalabrutinib plus venetoclax (or venetoclax with ibrutinib) do not require these resources. Patient experts also highlighted additional barriers to treatment for CLL, including travel and parking costs, lost income, childcare responsibilities and limited digital access. The

committee was aware that access to treatment options in the NHS is not an equality issue within its remit. But it noted that acalabrutinib plus venetoclax is an oral treatment so may be easier to use than some other treatments for CLL. It also noted that the company's target population for the evaluation excluded a minority of people who have untreated high-risk CLL (see section 3.3). It was aware that the marketing authorisation for acalabrutinib plus venetoclax included both high- and non-high-risk CLL subgroups. It was also aware that other fixed-duration treatment options are recommended for untreated CLL in adults irrespective of risk status (see section 3.2). So, it asked the company to provide evidence on acalabrutinib plus venetoclax in untreated high-risk CLL.

Uncaptured benefits

3.22 The company considered that the utility decrement applied for intravenous administration underestimated the burden on patients and NHS capacity. It said that this contributed to minimal quality-adjusted life year (QALY) differences between acalabrutinib plus venetoclax and venetoclax plus obinutuzumab. It also highlighted that acalabrutinib plus venetoclax may have a more favourable safety and tolerability profile than venetoclax plus ibrutinib and venetoclax plus obinutuzumab. But these differences were not reflected in the model because the applied utility decrements for adverse events were small. But the EAG explained that these proposed benefits were not supported by comparative health-related quality-of-life or patient-reported evidence and largely relied on company-led expert opinion. The EAG considered the rationale for an intravenous-related utility decrement to be reasonable but concluded that there was insufficient robust evidence to justify making changes to the model. The committee also acknowledged that venetoclax plus obinutuzumab administration would need additional hospital capacity because of the need for intravenous infusions of obinutuzumab, which was not the case for acalabrutinib plus venetoclax. It noted that a reduction in demand for intravenous infusions would reduce pressure on the healthcare system.

But given the substantial uncertainties in the evidence and modelling, the committee was unable to conclude whether there were uncaptured benefits associated with acalabrutinib plus venetoclax.

Conclusion

Recommendation

3.23 The committee concluded that because not all relevant comparators were included in the company submission:

- there was a high level of uncertainty in the comparative clinical evidence and economic modelling
- the treatment effect of acalabrutinib plus venetoclax compared with current standard care in the NHS was unknown
- it was not possible to determine a plausible cost-effectiveness estimate.

It could not determine whether acalabrutinib plus venetoclax is an acceptable use of NHS resources. So, acalabrutinib plus venetoclax could not be recommended for treating untreated non-high-risk CLL. The committee acknowledged that acalabrutinib plus venetoclax is a new treatment option that would be welcomed by healthcare professionals and people with CLL, so it encouraged the company to provide further evidence and analyses to address the uncertainties.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

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