NCPE Assessment Summary

Acalabrutinib (Calquence®)

HTA ID: 25040

24 July 2026

Applicant: Astra Zeneca

Acalabrutinib (Calquence®) in combination with venetoclax, with or without obinutuzumab, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of acalabrutinib (Calquence®) in combination with venetoclax, with or without obinutuzumab, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Following assessment of the Applicant's submission, the NCPE recommends that acalabrutinib (Calquence®) not be considered for reimbursement, for this indication. unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Astra Zeneca) Health Technology Assessment of acalabrutinib (Calquence®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In January 2026, Astra Zeneca submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of acalabrutinib (Calquence ®) in combination with venetoclax with obinutuzumab (AVO) or in combination with venetoclax without obinutuzumab (AV) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). Acalabrutinib is a selective inhibitor of Bruton tyrosine kinase (BTK). Acalabrutinib is taken orally as one 100mg film coated tablet, twice daily until disease progression, unacceptable toxicity or up to a max of fourteen 28-day cycles. Venetoclax is given for a total of twelve cycles. Obinutuzumab is given for a total of six cycles.

The population considered in this submission, i.e. those without the del(17p) or TP53 mutation, reflects a subpopulation of the full product licence. The comparator for this assessment was venetoclax in combination with obinutuzumab (VO) which was considered relevant for the Irish healthcare setting. Astra Zeneca is seeking reimbursement via the High-Tech Drug Arrangement.

1. Comparative effectiveness of acalabrutinib

AMPLIFY is an on-going phase III, randomised, open-label study which examines the efficacy and safety of acalabrutinib, in combination with venetoclax with or without obinutuzumab, compared to investigator's choice of chemoimmunotherapy (ICC) in adult patients with previously untreated CLL without the del(17p) or TP53 mutation. ICC was fludarabine with cyclophosphamide with rituximab (FCR) or bendamustine with rituximab (BR). Study completion is anticipated in early 2027.

The primary endpoint is progression free survival (PFS) assessed by blinded independent review committee (IRC). Overall survival (OS) was a key secondary endpoint.

Results for IRC-PFS and OS from the interim analysis (data cut off (DCO) 30 April 2024) were presented. A statistically significant benefit in IRC-PFS was observed in favour of both AV

versus FCR/BR (HR = 0.65 (95% CI 0.49, 0.87), p=0.00038) and AVO versus FCR/BR (HR= 0.42 (95% CI 0.30, 0.59), p<0.0001). The duration of benefit was not calculable for either comparison. A significant proportion of participants were censored.

Results from an updated OS analysis (DCO, 30 October 2024), which are published in the product licence and European Public Assessment Report (EPAR), were noted. These OS outputs were less favourable to AV (versus VO) than those from the 30 April 2024 DCO.

The Review Group note that AMPLIFY was not powered to detect a statistically significant difference in OS between the treatment groups, given the limited sample size and low number of OS events observed. OS data remain immature with a high degree of censoring across all treatment arms. Consequently, any extrapolations of these data are very uncertain.

There were no statistically significant differences, between any of the trial arms, in health-related quality of life measures (HRQoL). Participants reported lower HRQoL while on treatment, with values increasing following treatment cessation.

As there were no direct head-to-head trials comparing AV with VO or AVO with VO, an indirect treatment comparison (ITC) was required to estimate the relative effectiveness.

Comparative efficacy consisted of an unanchored simulated treatment comparison (STC) between AMPLIFY and an open label phase III randomised controlled trial (RCT) CLL14. CLL14 investigated VO (versus chlorambucil with obinutuzumab) in patients (with unrestricted cytogenetics) with previously untreated CLL and coexisting conditions. The STC indicated no statistically significant differences between AVO and VO for either OS or PFS. Estimated restricted mean survival time (RMST) differences (months) were: OS (AVO versus VO) = 0.4 (95% CrI -5.0, 5.7) and PFS (AVO versus VO) = -11.3 (95% CrI, -25.1, 2.5). For the comparison of AV versus VO, there was no statistical difference in OS (AV versus VO) = -0.4 (95% CrI, -9.5, 8.8); the RMST for PFS was significantly lower with AV than with VO = -10.9 (95% CrI,-20.4, -1.4)).

The Review Group highlighted the wide credible intervals observed across all comparisons

and considered overall the results of the STC to be very uncertain.

In addition, an anchored Bucher ITC was performed between AMPLIFY and an open label phase III RCT GAIA/CLL13. GAIA/CLL13 investigated first-line venetoclax combinations versus chemoimmunotherapy in patients with CLL without del(17p) or TP53 mutation. This ITC also indicated that there were no statistically significant differences between AV and VO and between AVO and VO for both PFS and OS.

The Review Group noted that the use of the OS results from the earlier DCO (30 April 2024) were used in the STC and ITC analyses. These were more favourable to AV than the later DCO.

2. Safety of drug

The proportion of participants experiencing one or more treatment emergent adverse events (TEAEs), across AMPLIFY study arms, was 53.6% in the AV arm, 69.4% in the AVO arm, and 60.6% in the FCR/BR arm. The most common Grade ≥ 3 TEAEs were neutropenia in all treatment arms (26.8% in the AV arm, 35.2% in the AVO arm, and 29.5%/35% in the FCR/BR arm). The proportion of participants who experienced treatment emergent serious adverse events (SAEs) was 24.7% in the AV arm, 38.4% in the AVO arm, and 27.4% in the FCR/BR arm. The SAEs with the highest incidence were COVID-19 pneumonia (AV arm: 5.8%; AVO arm: 11.3%), COVID-19 (AVO arm: 6.0%) and febrile neutropenia (FCR/BR arm: 8.1%).

The proportion of participants reporting TEAEs leading to discontinuation of any study treatment was greatest in the AVO arm (20.1%), followed by the FCR/BR arm (10.8%) and the AV arm (7.9%). Overall, 7.6%% of participants in the AV arm and 13.7% of participants in the AVO arm discontinued acalabrutinib due to TEAEs.

The SmPC carries special warnings for haemorrhage, infections, viral reactivation, cytopenias, second primary malignancies, atrial fibrillation, tumour lysis syndrome, and interstitial lung disease/pneumonitis.

3. Cost effectiveness of acalabrutinib

Methods

The cost-effectiveness model (CEM) compared AV to VO and also compared AVO to VO. The modelled population (i.e. those without the del(17p) or TP53 mutation) is a subpopulation of the full product licence, and may be younger than the population expected to receive treatment in Irish clinical practice. The semi-Markov state-transition cohort model had three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death. The treatment effects captured were the delay of disease progression and death. The key efficacy inputs were time to treatment discontinuation (TTD), time to progression (TTP), pre progression survival (pre-PS) and post progression survival (post-PS). Data from the AMPLIFY study (DCO: 30 April 2024) were used to inform treatment effectiveness in the first-line setting. Due to the immaturity of the post-PS data in AMPLIFY, the Applicant used data from the acalabrutinib arm of the ASCEND study to inform the post-PS state.

Overall, the Review Group highlighted that extrapolations predicting the long term PFS and OS benefit, based on the immature AMPLIFY study data, were very uncertain. Given the lack of statistical findings in the ITCs, the Applicant assumed equal efficacy between AV and VO, and between AVO and VO. As such, the costs and outcomes (QALYs) associated with VO differ according to the pairwise comparison (see Table 1). The Review Group consider that, given the uncertainty of the ITCs, equal efficacy cannot be robustly assumed.

Drug acquisition costs, drug administration costs, subsequent treatment costs, disease management costs, and adverse event costs were sourced from the published literature. HRQoL data was sourced from AMPLIFY.

Results

An incremental analysis of the costs and benefits of AV versus VO, and AVO versus VO was presented by the Applicant. Results of the Applicant's cost-effectiveness analyses are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results [a, b, c, d,]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
AV versus VO comparison					
VO	307,459	9.26			
AV	305,224	9.32	-2,235	0.05	-41,010 (Dominant)

AVO versus VO comparison					
VO	208,242	10.06			
AVO	258,378	10.08	50,137	0.01	5,006,217

AV: acalabrutinib + venetoclax; **AVO:** acalabrutinib + venetoclax + obinutuzumab; **CIC:** commercial in confidence; **ICER:** incremental cost-effectiveness ratio; **PAS:** patient access scheme; **QALY:** quality-adjusted life year; **VO:** venetoclax + obinutuzumab.
a Corresponding probabilistic ICER using 1,000 iterations for (i) AV versus VO comparison = -€60,919/QALY (Dominant); (ii) for AVO versus VO comparison = €5,352,638/QALY.
b Figures in the table are rounded, and so calculations may not be directly replicable.
c Discount rate of 4% was applied to costs and outcomes.
d A CIC PAS is on offer for acalabrutinib, and in place for venetoclax and obinutuzumab, which is not included in these results.

Sensitivity analysis

The probability of cost effectiveness of AV versus VO and AVO versus VO is shown in Table 2. Due to the previously discussed limitations, these probabilities do not reflect the full uncertainty associated with the analysis. Results should be interpreted with caution.

Table 2: Probability of cost effectiveness for AV/AVO versus VO [a, b]

	Probability of cost effectiveness
Threshold (€/QALY)	Applicant base case (costs corrected)
AV versus VO comparison	
20,000	60.10%
45,000	63.30%
AVO versus VO comparison	
20,000	0.10%
45,000	0.10%

AV: acalabrutinib + venetoclax; **AVO:** acalabrutinib + venetoclax + obinutuzumab; **NCPE:** National Centre for Pharmacoeconomics; PSA: probability of cost-effectiveness; **QALY:** quality-adjusted life year; **VO:** venetoclax + obinutuzumab.
a Results based on probabilistic analysis using 1,000 iterations.
b The results of the PSA are centred around the locus of four quadrants. As a result, the probability of cost effectiveness at the €20,000/QALY and €45,000/QALY thresholds are not linear.

The Review Group consider the assumption of equivalent efficacy to be a fundamental limitation of the analysis. It was not possible to address this limitation and, therefore, the Review Group did not present an NCPE adjusted base case Instead; scenario analyses were presented. The model was most sensitive to the implementation of a twelve-cycle treatment cap on VO and also to an increase in the model starting age from 59.9 years to 67.5 years.

A price-ICER analysis was conducted to estimate the reductions in the price to wholesaler of acalabrutinib (expressed as a total rebate on the PtW) that would be required for AVO to

meet the €45,000/QALY and €20,000/QALY thresholds. Analyses were conducted using Applicant base case assumptions. A price reduction of 85.4% and 85.8% would be needed to reach the €45,000/QALY and €20,000/QALY thresholds, respectively.

A price-ICER analysis was not implemented for the AV versus VO comparison, as under Applicant base case assumptions, AV is a dominant strategy (i.e. AV is more effective and less costly than VO).

4. Budget impact of acalabrutinib

The price to wholesaler (per 100mg pack) for acalabrutinib is €5462.81. The estimated cost, per patient, per treatment course, for AV and AVO is €125,368 and €146,161 (including VAT) respectively. The Applicant estimated that 229 incident patients would be diagnosed with CLL in Year One, rising to 246 incident patients in Year Five. Based on clinical opinion, the Applicant estimates that 90% of these patients do not have the del(17p) or TP53 mutation and so represent the subpopulation in which the Applicant is seeking reimbursement. VO is assumed to be the sole comparator. Based on internal estimates and clinical opinion, the Applicant estimates that both AV and AVO will jointly occupy 30% market share in Year One, rising each year to 55% in Year Five. The Applicant assumes a 70% and 30% split in uptake for AV and AVO respectively.

Under the Applicant assumptions, the five-year cumulative gross and net drug budget impacts, for the subpopulation who do not have the del(17p) or TP53 mutation, are about €63.11 million (including VAT) and €25.74 million (including VAT) respectively. Scenario analysis, which considered all patients eligible under the product licence (i.e. irrespective of del(17p) or TP53 mutation status), indicated that the five-year cumulative gross and net drug budget impacts would be about €70.12 million (including VAT) and €28.60 million (including VAT) respectively.

5. Patient Organisation Submission

A patient organisation submission was received from Chronic Lymphocytic Leukaemia Ireland.

6. Conclusion

This evaluation considered acalabrutinib, in combination with venetoclax, with or without obinutuzumab, for the treatment of adult patients (without the del(17p) or TP53 mutation) with previously untreated CLL.

The NCPE recommends that acalabrutinib not be considered for reimbursement, for this indication. unless cost-effectiveness can be improved relative to existing treatments.*

The full licensed population is broader than the subpopulation used to inform the cost-effectiveness analysis. The HSE may wish to consider implementing managed access should the decision be made to reimburse acalabrutinib here. Of note also, acalabrutinib is reimbursed for a different indication (i.e., as monotherapy, for the treatment of CLL in adults who have received at least one prior therapy).

*Next steps: The NCPE Assessment Report and recommendation will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.
Further information on this process may be found here.