NCPE Assessment Summary

Acalabrutinib (Calquence®)

HTA ID: 25041

18 August 2026

Applicant: AstraZeneca Ireland

Acalabrutinib in combination with bendamustine and rituximab for the treatment of adult patients with previously untreated mantle cell lymphoma who are ineligible for autologous hematopoietic stem cell transplantation.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of acalabrutinib (Calquence®), when given in combination with bendamustine and rituximab, for the treatment of adult patients with previously untreated mantle cell lymphoma who are ineligible for autologous hematopoietic stem cell transplantation.

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 (AstraZeneca Ireland) 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, AstraZeneca Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of acalabrutinib (Calquence®) in combination with bendamustine and rituximab (henceforth referred to as acalabrutinib + BR) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation (ASCT). AstraZeneca Ireland is seeking reimbursement of acalabrutinib on the High-Tech Drug Arrangement.

Acalabrutinib is a selective inhibitor of Bruton tyrosine kinase (BTK), which forms a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK activity. Acalabrutinib is taken orally at a dose of 100mg twice daily until disease progression or unacceptable toxicity. Bendamustine should be administered (via intravenous [IV] infusion) at 90mg/m^2 on day 1 and 2 of each 28-day cycle for a total of six cycles. Rituximab should be administered (via IV fusion) at 375mg/m^2 on day 1 of each 28-day cycle for a total of six cycles. Patients achieving a partial or complete response after the first six cycles, may receive maintenance rituximab at 375mg/m^2 on day 1 of every other cycle for a maximum of 12 additional doses. It is expected that acalabrutinib + BR will be used as a first-line treatment in adult patients with previously untreated MCL who are ineligible for ASCT, in line with the licensed indication. BR and R-CHOP (cyclophosphamide, doxorubicin, vincristine, rituximab, and prednisolone) are the current standard of care treatments included as comparators to acalabrutinib + BR.

1. Comparative effectiveness of acalabrutinib

ECHO is an ongoing, phase III, double-blind, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of acalabrutinib + BR versus placebo + BR in adult patients with previously untreated MCL who are ineligible for ASCT. Participants were randomised to receive acalabrutinib + BR or placebo + BR for six 28-day cycles. After six cycles, participants who achieved at least a partial response receive maintenance rituximab every other cycle (for a maximum of 12 additional doses, until cycle 30) in addition to acalabrutinib or placebo. From cycle 31, participants receive acalabrutinib monotherapy or placebo monotherapy until disease progression or unacceptable toxicity. The primary endpoint was progression-

free survival (PFS) assessed by independent review committee (IRC). Overall survival (OS) was a key secondary endpoint. Both the primary and secondary endpoints were assessed using the full analysis set (FAS).

At the interim analysis (median follow-up 44.9 months; 46.1 months in the acalabrutinib + BR arm; 44.4 months in the placebo + BR arm, February 2024 data cut), the ECHO trial achieved its primary endpoint. There was a statistically significant improvement in PFS in participants who received acalabrutinib + BR compared with those who received placebo + BR (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57 to 0.94; p=0.016). Median IRC-assessed PFS was reached in both treatment arms. There was no statistically significant difference in OS between the acalabrutinib + BR and placebo + BR arms (HR 0.86; 95% CI 0.65 to 1.13; p=0.2743). At the second data cut with an additional 12 months follow-up, a statistically significant PFS benefit (FAS population: HR: 0.68; 95% CI 0.53 to 0.87; p=0.002) remained. For OS there was no statistically significant benefit (HR: 0.86; 95% CI 0.66 to 1.13; p=0.2742) observed, consistent with the earlier data cut. ECHO trial data are immature (37% maturity) and median OS was not reached in either arm.

The ongoing ECHO trial commenced during the COVID-19 pandemic and to evaluate the potential impacts of COVID-19 deaths on the treatment effect of acalabrutinib + BR, the Applicant conducted prespecified sensitivity analyses censoring COVID-19 deaths. These sensitivity analyses showed improvements compared with the FAS population for PFS (HR 0.64; 95% CI 0.48 to 0.84; p=0.0017) and OS (HR 0.75; 95% CI 0.53 to 1.04; p=0.079). The Review Group note that while there may have been excess deaths directly related to COVID-19 at the beginning of the pandemic, it is unlikely that there will be much difference between the expected deaths due to COVID-19 in the future and those in the final years prior to the February 2024 data cut, as COVID-19 is now considered endemic. The Review Group consider censoring of deaths, outside of the peak pandemic period in particular, to be inappropriate and the Applicant did not provide sufficient information regarding the censoring of COVID-19 deaths in the trial. As a consequence, the Review Group do not know how many deaths were censored due to COVID-19 in the years where COVID-19 has been endemic, and the vaccination status of patients who died. Therefore, the Review Group consider the FAS analysis to be more appropriate in the NCPE adjusted base

case analysis.

2. Indirect Treatment Comparison

Head-to-head trials were not available to provide direct comparative evidence for acalabrutinib + BR versus R-CHOP. Therefore, indirect comparative methods were required to derive relative effectiveness estimates of acalabrutinib + BR, BR, and R-CHOP. The outcomes of interest for the indirect treatment comparison (ITC) were PFS and OS and three trials were eligible for inclusion (ECHO, BRIGHT and StiL NHL1), which differed in trial design, eligibility criteria, control arm treatments and maintenance rituximab treatment. These differences may introduce between-trial heterogeneity to the ITCs. For PFS (studies=3), fixed and random effects ITCs were performed using BR as the reference treatment in the network. For OS (studies=2), only fixed effects ITCs were performed as a limited number of studies had reported OS (n=1 for each comparison). Due to the limited size of the network, as well as the absence of loops, it was not feasible to assess consistency between direct and indirect effect estimates in the ITC. Results of the fixed effects analysis indicated a statistically significant PFS benefit for acalabrutinib + BR versus R-CHOP and BR. For OS, the fixed effect analysis showed a numerically favourable benefit for acalabrutinib + BR versus R-CHOP; however, the result was not statistically significant.

3. Safety of acalabrutinib

The safety profile of acalabrutinib was based on the safety analysis set in ECHO, which consisted of randomised participants who received at least one dose of study drug. Most participants experienced at least one treatment-emergent adverse event (TEAE) (acalabrutinib + BR: 99.7%; placebo + BR: 99.0%). Grade ≥3 TEAEs were comparable between treatment arms (acalabrutinib + BR: 88.9%; placebo + BR: 88.2%). Among these, 66.3% and 64.0%, respectively, were identified as Grade ≥3 treatment-related TEAEs. The majority of treatment-related TEAEs were experienced by a greater proportion in the acalabrutinib + BR arm compared with the placebo + BR arm. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were neutropenia, rash, thrombocytopenia, anaemia, pneumonia, second primary malignancies, hypertension and second primary malignancies excluding non-melanoma skin cancer.

4. Cost effectiveness of acalabrutinib

Methods

A three-state partitioned survival model was submitted, comprising three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death. The treatment effects captured by the model were the delay of disease progression and death. Clinical data for acalabrutinib + BR and BR was obtained from ECHO (February 2024 data cut). The Applicant base case utilised the COVID-19 censored dataset from ECHO, whereas the NCPE adjusted base case utilised the FAS dataset (for reasons discussed in section 1) to inform the extrapolation of OS, PFS, and time-to-treatment discontinuation (TTD)

Parametric survival curves were fitted to patient-level data from ECHO for OS, PFS and TTD for acalabrutinib + BR and BR. The Applicant considered joint parametric models to be most appropriate and selected the exponential distribution to extrapolate PFS and the gamma distribution to extrapolate OS, which the Review Group consider appropriate. The Applicant base case used the Weibull curve to extrapolate TTD for acalabrutinib, while the NCPE adjusted base case used the log-logistic TTD curve, as it was the best fitting in the FAS. A cap was also applied to all treatment discontinuation curves in the model, such that time on treatment does not exceed PFS over the time horizon, which the Review Group consider to be appropriate. Following acalabrutinib + BR or BR, patients with complete or partial response in ECHO received maintenance rituximab every other cycle (in addition to acalabrutinib or BR) for up to 12 additional cycles, followed by acalabrutinib monotherapy or placebo monotherapy thereafter until disease progression or unacceptable toxicity. The TTD Kaplan Meier (KM) curves for rituximab showed that almost all patients had discontinued by the end of the trial follow-up. Therefore, KM estimates were used directly in the model, and no extrapolations were needed. The OS, PFS, and TTD curves in the model were adjusted for background mortality to ensure that for every cycle, event risks were always greater than or equal to the risk of death in the age- and sex-matched general population.

PFS and OS efficacy estimates for R-CHOP were derived from the results of the ITC. The Applicant used the HRs derived from the ITC which censored COVID-19 deaths in ECHO in the base case, while the NCPE adjusted base case used the ECHO FAS (as discussed in Section 1). For TTD, an assumption was made that TTD for R-CHOP can be estimated by applying the same HR as that used for PFS versus BR, which the Review Group considers to be reasonable.

Relative dose intensities (RDI) of 89% and 94% were applied to acalabrutinib and ibrutinib (a subsequent treatment) in the Applicant base case. These were adjusted to 100% in the NCPE adjusted base case as not all factors which lead to reduced drug exposure in a clinical trial (in ECHO, this was due to adverse events [AEs]) will lead to a reduction in drug costs in practice. In particular for drugs dispensed on the High-Tech Drug Arrangement whereby, the full cost is incurred by the HSE upon dispensing. Given acalabrutinib is a long-term treatment with no fixed duration, the risk of AEs beyond the trial period are expected to be low as these would be managed overtime. The Review Group also modified the treatment duration of ibrutinib to 17.7 months based on KM TTD data for ibrutinib sourced from the RAY and SPARK trials, which evaluated the efficacy of ibrutinib in patients with relapse or refractory MCL. The IV chemotherapy administration cost was also corrected for R-CHOP in the NCPE adjusted base case.

In the Applicant base, the PF utility (health related quality of life) value (0.830) derived from ECHO was used to inform the PF health state utility value. The PD health state utility value (0.730) was estimated by using the difference between the PF and PD utility values used in a prior NICE appraisal (TA502) in patients with relapsed or refractory MCL. The Review Group considered the values from NICE TA370 to be more appropriate as the LYM-3002 trial (utilised in NICE TA370) investigated bortezomib in patients with newly diagnosed MCL who were ineligible or not considered for ASCT. This is similar to the population of interest for acalabrutinib, which assumes a smaller difference between the PF and PD health states. Additionally, the NCPE adjusted base case used the UK EQ-5D-3L value set as the preferred method of measuring health-related quality of life instead of the Irish EQ-5D-5L value set used in the Applicant's base case. In the NCPE adjusted base case, the PF utility value estimated from ECHO exceeds those of the age- and sex-matched general population using the UK EQ-5D-3L value set. Thus, this PF utility value was capped by the general population utility value (0.776) for the entire model time horizon and the PD health state utility value in the NCPE adjusted base case was 0.705.

Results

The incremental analyses of the costs and benefits of acalabrutinib + BR versus BR and

versus R-CHOP were presented by the Applicant. The Review Group noted the probabilistic results are notably different to the deterministic results in both the Applicant base case (versus both BR and R-CHOP) and the NCPE adjusted base case (versus R-CHOP only). Therefore, the results of both the probabilistic and the deterministic incremental cost-effectiveness ratios should be considered with a degree of caution.

Table 1 : Applicant base case incremental cost-effectiveness results (Acalabrutinib + BR vs BR and vs R-CHOP) [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BR	161,911	6.32	-	-	-
Acalabrutinib + BR	348,769	7.06	186,858	0.73	254,746
R-CHOP	196,782	5.72	-	-	-
Acalabrutinib + BR	348,769	7.06	151,987	1.34	113,406

BR: bendamustine + rituximab; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **R-CHOP:** cyclophosphamide, doxorubicin, vincristine, rituximab, and prednisone;
[a] Corresponding probabilistic ICER using 5,000 iterations=€296,250/QALY (versus BR); =€132,378/QALY (versus R-CHOP). Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% is applied to costs and outcomes.
[b] A commercial in confidence patient access scheme applies to acalabrutinib, not included in this table.

The NCPE Review Group identified several limitations in the Applicant's base case and have made changes in the NCPE adjusted base case (Table 2). These include using the FAS population to inform the efficacy and comparative effectiveness of acalabrutinib + BR, BR, and R-CHOP; the UK EQ-5D-3L utility value set; TA370 as the source of the difference between the PF and PD utility value; an ibrutinib treatment duration of 17.7 months; a 100% RDI for acalabrutinib and ibrutinib; a corrected R-CHOP IV treatment administration cost; and a log-logistic TTD extrapolation curve for acalabrutinib + BR.

Table 2: NCPE adjusted base case incremental cost-effectiveness result (Acalabrutinib + BR vs BR and vs R-CHOP) [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BR	131,263	4.99	-	-	-
Acalabrutinib + BR	355,090	5.42	223,827	0.43	515,334
R-CHOP	160,127	4.44	-	-	-
Acalabrutinib + BR	355,090	5.42	194,963	0.98	199,047

BR: bendamustine + rituximab; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **R-CHOP:** cyclophosphamide, doxorubicin, vincristine, rituximab, and prednisone;
[a] Corresponding probabilistic ICER using 5,000 iterations=€541,715/QALY (versus BR); =€247,711/QALY (versus R-CHOP). Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% is applied to costs and outcomes.
[b] A commercial in confidence patient access scheme applies to acalabrutinib, not included in this table.

Sensitivity analysis

The probability of cost-effectiveness for acalabrutinib + BR versus BR and versus R-CHOP in the NCPE adjusted base case was 0% at thresholds of €20,000 per QALY and €45,000 per QALY. A price-ICER analysis, using NCPE adjusted base case assumptions, indicated that a 80% and 84% reduction to the price to wholesaler (PtW) of acalabrutinib would be required for it to be cost-effective at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus BR). A 62% and 70% reduction to the PtW of acalabrutinib would be required for it to be cost-effective at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus R-CHOP). These estimates were done using the deterministic results and likely underestimate the discounts required.

The probability of cost-effectiveness for acalabrutinib + BR versus BR in the Applicant base case was 0% at both thresholds (€20,000 per QALY and €45,000 per QALY). The probability of cost-effectiveness for acalabrutinib + BR versus R-CHOP in the Applicant base case was 0% at the threshold of €20,000 per QALY and <0.3% at the threshold of €45,000 per QALY.

5. Budget impact of acalabrutinib

The PtW for one pack (60 film-coated tablets) of acalabrutinib 100mg is €5,447.43 (VAT not applicable). The estimated total cost, per patient, per year of acalabrutinib + BR is €85,768 (including VAT). Patients with incident MCL who are unfit for ASCT in Ireland were assumed to be the eligible population for acalabrutinib + BR. In a world without acalabrutinib + BR, the Applicant assumed the treatment distribution between BR and R-CHOP is equal (50:50). Following the introduction of acalabrutinib + BR, the Applicant estimated a market share of 20% in year one, increasing to 40% by year five, with acalabrutinib + BR projected to displace BR only. The Applicant assumed patients received a mean of 34.82 cycles of acalabrutinib (28-day cycles) estimated from a mean treatment duration of 32.5 months derived from ECHO. BR and R-CHOP were assumed to be received for six cycles. Based on the Applicant's preferred assumption, the five-year cumulative gross drug-budget impact including VAT was €8.4 million, and the five-year cumulative net drug-budget impact including VAT was €6.9 million.

The mean treatment duration of acalabrutinib estimated from the cost-effectiveness model (CEM) was 67.61 months or 72.44 cycles (28-day cycles) derived from the Applicant base

case TTD curve and 64.44 months or 69.04 cycles derived from the NCPE base case TTD curve. According to the SmPC, and clinical opinion, treatment with acalabrutinib should be continued until disease progression or unacceptable toxicity. The mean treatment duration, derived from the CEM better reflects the expected treatment duration in clinical practice and was applied in the NCPE-adjusted base case and capped at five years to align with the budget impact model forecast. In the NCPE-adjusted base case, the five-year cumulative gross drug-budget impact including VAT was €10.3 million, and the five-year cumulative net drug-budget impact including VAT was €8.8 million.

6. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment

7. Conclusion

The NCPE recommends that acalabrutinib + BR not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*Next steps: The NCPE Assessment Report (and) recommendation (and Patient Organisation submission), 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.