6.01 ACALABRUTINIB, Tablet 100 mg, Calquence®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (Telephone/Online) listing for acalabrutinib in combination with bendamustine and rituximab for patients with previously untreated Stage III or IV mantle cell lymphoma (MCL) who are ineligible for stem cell transplantation.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus bendamustine and rituximab treatment alone.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with previously untreated Stage III or IV mantle cell lymphoma who are ineligible for ASCT.
Intervention	Induction (Cycles 1–6): acalabrutinib 100 mg orally twice daily for 6 cycles, bendamustine 90 mg/m^2 IV on Days 1 and 2 for 6 cycles, and rituximab 375 mg/m^2 on Day 1 for 6 cycles. Continuing therapy (Cycle 7 onwards): Patients achieving partial response or better after induction continue to receive acalabrutinib 100 mg orally twice daily, and up to 12 doses of rituximab 375 mg/m^2 once every 8 weeks, up to Cycle 30.
Comparator	Induction (Cycles 1–6): bendamustine 90 mg/m^2 IV on Days 1 and 2 for 6 cycles, and rituximab 375 mg/m^2 on Day 1 for 6 cycles. Continuing therapy (Cycle 7 onwards): Patients achieving partial response or better after induction receive up to 12 doses of rituximab 375 mg/m^2 once every 8 weeks, through no later than Cycle 30.
Outcomes	Progression free survival, overall response rate, overall survival, duration of response, time to response, patient reported outcomes, safety.
Clinical claim	In patients with previously untreated Stage III or IV mantle cell lymphoma, acalabrutinib in combination with bendamustine and rituximab is superior in terms of efficacy and inferior in terms of safety when compared to bendamustine and rituximab.

Source: Table 1-1, p5 of the submission.
Abbreviations: ASCT, autologous stem cell transplant; IV, intravenous.
Note: Cycle length is 28 days. Patients receive acalabrutinib/placebo until disease progression or unacceptable toxicity.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. The application for acalabrutinib in combination with bendamustine and rituximab was evaluated through Project Orbis, with the proposed indication for the treatment of adult patients with previously untreated MCL. No TGA regulatory documents were available at the time of the evaluation. The TGA Delegate's Overview, received prior to the PBAC meeting, stated that the Delegate proposed to approve registration for the following indication: acalabrutinib 'in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated MCL who are

not eligible for autologous haematopoietic stem cell transplantation'. The Delegate proposed 'to impose a condition of registration that requires submission of subsequent pre-planned and final OS analyses from ECHO. These should be assessed to ensure continuing absence of evidence of survival detriment at final analysis.'

Previous PBAC considerations

2.2 The PBAC has not previously considered acalabrutinib for the treatment of patients with previously untreated Stage III or IV MCL.

2.3 There have been 7 previous submissions to the PBAC for acalabrutinib for 3 different indications: relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic leukaemia (CLL/SLL; recommended March 2020 PBAC meeting, PBS listed September 2020; change to Deed of Agreement not recommended March 2023), relapsed/refractory MCL (recommended July 2021 PBAC meeting, PBS listed February 2022), and first line CLL/SLL (not recommended July 2020, November 2021, December 2022, recommended July 2024, PBS listed January 2024).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
Acalabrutinib 100 mg tablet, 56	$7,414.57 published price $[redacted] effective price	1	56	5	Calquence
Category / Program: General Schedule					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)					
Severity: Stage III or IV mantle cell lymphoma					
Condition: Mantle cell lymphoma					
Indication: Previously untreated Stage III or IV mantle cell lymphoma					
Treatment Phase: First line drug treatment of this indication					
Clinical criteria:					
The condition must be untreated with drug treatment at the time of the first dose of this drug					
AND					
Clinical criteria:					
Patients must have a WHO performance status of 2 or less					
AND					
Clinical criteria:					
Patient must not be eligible for stem cell transplantation					
Treatment criteria:					
Patient must be undergoing induction treatment with this drug, in combination with bendamustine and rituximab for six cycles					
OR					
Treatment criteria:					
Patient must be undergoing continuing treatment with this drug - the condition has not progressed while the patient has actively been on this drug					

3.1 The proposed published AEMP ($7,251.97) and DPMQ ($7,414.57) were consistent with other PBS-listed indications for acalabrutinib. The submission proposed a special pricing arrangement for the proposed indication, with an effective AEMP of $[redacted] and DPMQ of $[redacted].

3.2 The requested restriction was narrower than the submission's proposed TGA indication, with additional requirements for patients to be ineligible for stem cell transplantation (refer to paragraph 2.1 for the indication proposed for registration by the TGA Delegate) and with a WHO performance score of 2 or less. The requested restriction was generally consistent with the clinical evidence presented in the submission, however the ECHO trial excluded patients under the age of 65, and did not explicitly require patients to be ineligible for stem cell transplantation. The ESC noted that overall the restriction was loosely consistent with the trial population, which excluded patients for whom the goal of therapy was tumour debulking before stem cell transplant. The ESC also considered that a clinical criterion should be added to the restriction that the condition must be symptomatic, as patients with indolent

disease may not have symptoms. The Pre-Sub-Committee Response (PSCR) indicated no objections to the addition of this criterion.

3.3 The proposed treatment criteria state that acalabrutinib must initially be in combination with bendamustine and rituximab for a six-cycle induction phase, followed by continuing treatment with acalabrutinib until disease progression, consistent with the ECHO trial. The submission stated that continuing treatment could consist of acalabrutinib monotherapy or combination therapy with rituximab, however the evaluation noted that rituximab maintenance treatment is not specified in the proposed continuing treatment criterion. The ESC considered this was appropriate and gives clinicians flexibility in the choice of maintenance therapy. The ESC also considered it would be appropriate for the acalabrutinib restriction to align with the restriction for bendamustine.

3.4 The submission indicated that flow-on changes would be required to the bendamustine PBS restriction (PBS item codes: 10760H and 10763L), suggesting that the relevant clinical criterion be amended from 'The treatment must be in combination with rituximab' to 'The treatment must be in combination with rituximab, or in combination with rituximab and acalabrutinib'. There will be no flow on changes required for rituximab as it has an unrestricted PBS listing.

3.5 The current PBS restrictions for Bruton tyrosine kinase (BTK) inhibitors in the relapsed/refractory MCL setting stipulate that patients must be untreated with BTK inhibitors (acalabrutinib, ibrutinib or zanubrutinib) or must have developed intolerance to another BTK inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication. This means that patients receiving acalabrutinib as first line therapy for MCL will not be eligible to receive treatment with BTK inhibitors in the relapsed/refractory setting. The submission stated that this is consistent with clinical practice, especially since acalabrutinib is used until disease progression. The evaluation noted that the ECHO trial permitted subsequent BTK inhibitor use after patients ceased their study treatment, including those in the acalabrutinib arm of the trial. The evaluation considered that the management of patients with mantle cell lymphoma was evolving, and the role of BTK inhibitors in patients relapsed/refractory to a BTK inhibitor in the first line setting is unclear. However, the ESC considered it was reasonable to restrict BTK inhibitor listings to once in a lifetime as there was no evidence of benefit with repeated use. The ESC considered that the 4.3% of patients in the ECHO trial who used BTK inhibitors post progression, was likely similar to the proportion of patients in clinical practice that may, despite the restriction, continue use of acalabrutinib post progression with some perceived clinical benefit (discussed in paragraph 6.43).

3.6 The PSCR requested PBAC to advise whether acalabrutinib should be permitted in patients who develop a contraindication or intolerance necessitating permanent treatment withdrawal of bendamustine and/or rituximab during the induction phase. The ESC considered that this was appropriate if the intention and commencement of treatment is with ABR. Only a small number of patients would be intolerant.

3.7 The submission stated that a patient access program for acalabrutinib in patients with previously untreated MCL is planned to commence upon TGA registration. The submission estimated approximately < 500 patients will join the patient access program, and these patients would be able to transition to PBS-listed acalabrutinib under the proposed restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 MCL is a rare and often aggressive type of B cell non-Hodgkin lymphoma that comprises approximately 5% of all newly diagnosed non-Hodgkin lymphomas (Xie 2022, Barraclough 2025). It is 3 times more common in men than women, and occurs more commonly in older people, with 62% of patients aged 65 years or older at initial presentation (median age 72 years; Epperla 2018, Hess 2022), and is typically aggressive (in 85% to 90% of patients) while the remainder have indolent disease (Silkenstedt and Dreyling 2023). In Australia, 330 patients were diagnosed with MCL in 2020 (Australian Institute of Health and Welfare 2024). The ESC noted that although the majority of cases are aggressive, some are indolent.

4.2 Because patients tend to be asymptomatic in early stages, over 80% have advanced disease (i.e. Stage III or IV) at diagnosis. However, persistent swelling of lymph nodes, especially in the neck and throat region, or in the armpits and groin may lead patients to seek medical attention. Patients may also report non-specific symptoms including lack of appetite, nausea, vomiting, indigestion, satiety, abdominal swelling or bloating, and abdominal pain or discomfort (Leukaemia Foundation 2024). At advanced stages when the disease has spread to the gastrointestinal tract, bone marrow or liver, patients may present with fever, night sweats, unexplained weight loss and fatigue (Leukaemia and Lymphoma Society 2024).

4.3 MCL is considered incurable. The aim of first line treatment is to achieve remission and remove the risk of relapse, with the current choice of first line treatments dependent on symptoms and the patient's ability to tolerate aggressive induction therapy and/or autologous stem cell transplant (ASCT). Patients diagnosed at the early stages of disease may be treated with radiotherapy alone or chemotherapy with or without radiotherapy. For advanced-stage patients suitable for intensive therapy and ASCT, rituximab and cytarabine containing chemo-immunotherapy induction followed by ASCT consolidation and maintenance rituximab remains the current standard of care (Barraclough 2025, Dreyling 2017, McKay 2018). For older patients, or those who are transplant-ineligible, the standard of care induction therapy is bendamustine in combination with rituximab, which was PBS listed for first line treatment of MCL in May 2016. Barraclough (2025) notes that evidence for the use of maintenance rituximab therapy for transplant ineligible patients is less clear. The evaluation noted that use of maintenance rituximab after induction with bendamustine and rituximab is included in eviQ treatment recommendations for transplant-ineligible patients.

4.4 The submission positioned acalabrutinib with bendamustine and rituximab as an alternative to bendamustine and rituximab induction in previously untreated patients with Stage III or IV MCL who are ineligible for ASCT.

4.5 The submission and the ESC noted that the treatment landscape for MCL is rapidly changing, particularly with regard to the diminishing role of ASCT in younger patients, and growing evidence of BTK inhibitors as an effective first line treatment, either in combination with rituximab or with chemo-immunotherapy. The submission argued that the criterion of 'transplant eligibility' may eventually be less important, and more patients will be eligible for acalabrutinib with bendamustine and rituximab if ASCT is no longer considered standard of care. The evaluation considered that the potential for use outside the proposed PBS restriction in the ASCT-eligible population may increase if BTK inhibitors become a preferred first line treatment for these patients.

4.6 Acalabrutinib is a small-molecule BTK inhibitor. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated placebo in combination with bendamustine and rituximab induction followed by rituximab maintenance as the main comparator. The main arguments provided in support of this nomination were that this treatment: is the standard of care in Stage III or IV MCL patients who are transplant ineligible; is the most widely used regimen in Australian clinical practice; and is consistent with the comparator arm in the ECHO trial. The evaluation considered that bendamustine and rituximab induction followed by rituximab maintenance is an appropriate comparator.

5.2 In addition, based on the current restriction wording for BTK inhibitors for relapsed/refractory MCL, use of a PBS-listed BTK inhibitor would not be permitted after first line use of acalabrutinib (as discussed in paragraph 3.5). A reduction in subsequent treatment with a BTK inhibitors after first line acalabrutinib use was incorporated into the economic analysis (applied to costs only, with no impact on clinical outcomes) and financial estimates. The ESC noted that post progression treatment will be different for acalabrutinib with bendamustine and rituximab, versus bendamustine and rituximab only, as patients who received acalabrutinib in the first line setting would not be able to receive a BTK inhibitors in the second line setting.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with acalabrutinib including that it prolongs response to first line therapy, and is a tolerable, oral therapy for transplant ineligible patients, including those in rural and regional locations. The PBAC comments outlined that MCL is incurable and that there was a need for more effective treatment options for transplant ineligible patients in the first line setting.

6.3 The PBAC noted that some of the comments outlined potential uses for acalabrutinib which were outside the submission's proposed restriction including as initial monotherapy in elderly patients, and as part of induction in transplant eligible patients. The PBAC noted that such uses were not supported by the trial data.

6.4 The PBAC noted the advice received from Lymphoma Australia, Leukaemia Foundation, and Rare Cancers Australia describing the impacts of MCL including extreme fatigue, swollen glands, chronic pain, stress, mental struggle, and reduced capacity for work and daily living (e.g. going to the shops). Input also noted the impacts of current chemotherapy regimens including extreme nausea, vomiting, hair loss and "brain fog". The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 The submission was based on one head-to-head trial comparing acalabrutinib in combination with bendamustine and rituximab to placebo with bendamustine and rituximab in patients with previously untreated MCL (ECHO).

6.6 Details of the ECHO trial are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ECHO	A phase 3, randomised, double-blind, placebo-controlled, multicenter study of bendamustine and rituximab (BR) alone versus in combination with acalabrutinib (ACP-196) in subjects with previously untreated mantle cell lymphoma (ECHO; ACE-LY308 / NCT02972840).	Clinical Study Report – Interim Analysis based on data cut-off of 15 February 2024
	Wang M, *et al*. A phase 3 study of acalabrutinib plus bendamustine and rituximab in elderly (aged ≥65 years) treatment-naïve patients with mantle cell lymphoma.	*Hematol Oncol* 2019; 37: 554-555. (conference abstract)

Source: Table 2-3, p31 of the submission.

6.7 The key features of the ECHO trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ECHO	598	Randomised, placebo-controlled, double blind, multicentre trial. 5.52 months induction followed by maintenance until disease progression	Unclear	Patients aged ≥65 with previously untreated mantle cell lymphoma, ECOG status ≤2	PFS, OS, best ORR, duration of response, time to response, EQ-5D-5L, safety	PFS, OS, time on treatment, time to first subsequent therapy, use of subsequent treatments, EQ-5D-5L, adverse events

Source: Section 2.3, pp33-38 of the submission.
Abbreviations: European Cooperative Oncology Group; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

6.8 The ECHO trial (N=598) is a multicentre, randomised, placebo-controlled trial to evaluate the efficacy and safety of acalabrutinib in combination with bendamustine and rituximab compared to placebo in combination with bendamustine and rituximab in patients aged ≥65 with previously untreated MCL. The submission noted that the ECHO trial is ongoing, with study completion estimated to be October 2025, though the PSCR advised that final results are now expected in 2027. The results presented in the submission were from an interim analysis with a data cut-off of 15 February 2024.

6.9 The submission noted that 635 patients were originally randomised in the trial. However, only 598 (94.2%) of the randomised patients were included in the interim analysis, as 37 patients (all from China) were excluded due to having less than 2 years of follow-up at the time of the data cut-off. However, the evaluation noted that the full analysis set in the ECHO clinical study report, defined as all randomised patients who received at least one dose of the study drug, was also based on 598 randomised patients (n=299 in each treatment arm). No further details of the excluded patients were provided in the submission. The ECHO trial Statistical Analysis Plan stated that patients from the China cohort who had been randomised for at least 24 months prior to the data cutoff for the interim analysis would be unblinded and included in the full analysis set. Analysis of the full cohort of Chinese patients was planned after all patients in this cohort had completed their enrolment, with results summarised in a separate clinical study report. Consequently, the evaluation considered that the ECHO trial had an overall unclear risk of bias. The PSCR stated that these patients were still receiving rituximab, with or without acalabrutinib, and had not completed their treatment regimen, making it premature to unblind them.

6.10 The ECHO trial enrolled patients aged ≥65 years with pathologically confirmed MCL and ECOG performance status of ≤2 who had not received prior treatment with systemic anticancer therapies. Patients were excluded if the goal of their treatment was tumour debulking before stem cell transplant. The trial inclusion/exclusion criteria did not specify that patients must be ineligible for stem cell transplant, which was inconsistent with the submission's proposed restriction for acalabrutinib. While it is likely that many patients in the trial would be ineligible for stem cell transplant given their age and exclusion criteria for tumour debulking prior to transplant, the evaluation considered it possible that not all patients in the trial were transplant ineligible. The ESC considered that the intent of the clinical trial was effectively the

same as the PBS population, noting that plans regarding ASCT can change during treatment, and that the definition of ASCT eligibility is at clinician discretion.

6.11 The majority of enrolled patients were White (78.3%) or Asian (15.6%) and male (70.7%) with an average age of 71.6 years and an ECOG performance status of 0 (49.5%) or 1 (43.6%). The majority of patients (95.2%) had Stage III/IV disease, with a small number of patients classed as having Stage I/II disease (4.8%). Patients with Stage I or II disease would not be eligible for treatment with acalabrutinib under the submission's proposed restriction. Simplified MCL International Prognostic Index (MIPI) score classifications (a weighted summation of age, ECOG performance status, lactate dehydrogenase and white cell count) were low, medium or high risk in 33.4%, 42.3%, and 24.2% of patients, respectively. Mean time from diagnosis to randomisation in the trial was 4.1 months and the mean time from randomisation to first dose was 2.2 months. Baseline characteristics were well balanced between treatment arms. The ESC considered the clinical trial population generally representative of the proposed population.

6.12 Patients in the ECHO trial received acalabrutinib 100 mg or placebo twice daily, both in combination with bendamustine and rituximab, for 6 × 28 day induction cycles. From Cycle 7, patients who were tolerating treatment and had not experienced disease progression continued to receive acalabrutinib or placebo monotherapy. In addition, patients who had achieved a partial response or better received rituximab on Day 1 of every other cycle (starting on the next even-numbered cycle after completion of induction therapy) up to Cycle 30. Beyond Cycle 30, patients continued to receive acalabrutinib or placebo monotherapy until progressive disease or unacceptable toxicity.

6.13 Throughout the trial, any patients in the placebo arm who had progressive disease were allowed to cross over to receive acalabrutinib monotherapy. Patients in either treatment arm could receive subsequent treatment with other MCL treatments (including BTK inhibitors) after study treatment completion or discontinuation. At least one subsequent MCL treatment was received by 30 (10.0%) patients in the acalabrutinib arm and 88 (29.4%) patients in the placebo arm, of whom 13 patients (43% of subsequent therapy use, or 4.3% of total) in the acalabrutinib arm and 76 (86.4%) in the placebo arm received a BTK inhibitor (inclusive of the 51 patients who crossed over from placebo to acalabrutinib after disease progression as specified in the trial protocol). The evaluation noted that based on the current restriction wording for BTK inhibitors for relapsed/refractory MCL, use of any PBS-listed BTK inhibitor would not be permitted after first-line use of acalabrutinib, and costs of subsequent BTK inhibitors were not included in the acalabrutinib arm of the economic model.

6.14 The submission noted that the ECHO trial was conducted during the COVID-19 pandemic, with the interim analysis inclusive of patients who received treatment between May 2017 and March 2023. During this time there were a total of 97 deaths in the acalabrutinib arm and 106 deaths in the placebo arm, with a cause of COVID-19 (confirmed or suspected) nominated for 33 (34%) and 26 (25%) of the deaths in the

acalabrutinib and placebo arms, respectively. The submission stated that the ECHO trial data were censored to adjust for excess COVID-19 deaths to more accurately represent the present-day situation. Results for progression free survival and overall survival from the ECHO trial were presented for both the full analysis set and the analysis that censored for COVID-19 related deaths (excluding patients with death related to COVID-19, and without disease progression prior to death for the progression free survival endpoint). Censoring patients with deaths related to COVID-19 resulted in more favourable outcomes for the acalabrutinib arm versus the placebo arm of the trial, given the higher proportion of deaths in the acalabrutinib arm. The evaluation considered that this may be the result of acalabrutinib patients being at greater risk of infection, with greater immunosuppression associated with ongoing use of acalabrutinib. The PSCR stated that the addition of acalabrutinib to bendamustine and rituximab increases the extent of immunosuppression, as acalabrutinib interferes with normal B-cell function leading to additional cumulative toxicity compared to bendamustine and rituximab alone, and indicated that the more deadly strains of COVID-19 viruses in a partially vaccinated patient population during the global pandemic had a greater impact on immunosuppressed patients than the present environment.

6.15 The evaluation considered it was unclear whether the analyses censored for COVID-19 related deaths would be representative of outcomes in current clinical practice, given causes of death are a competing risk. The ESC considered that the full analysis set (without censoring for COVID-19) should be used for both the clinical and economic evaluations, as the analysis censoring for COVID-19 related deaths does not account for competing causes of death, and favours acalabrutinib. The Pre-PBAC response contended that the impact of the COVID-19 censored analysis "is not necessarily confounded by the competing risks of other causes of death. Rather, the COVID-19 analysis seeks to account for the timing of those deaths given that deaths related to COVID-19 were brought forward in time from when they otherwise would have occurred in the absence of the pandemic." The Pre-PBAC response included an inverse probability of censoring weights (IPCW) analysis to provide estimates of the treatment effect in the presence of informative censoring, which it claimed supported the simple censoring approach conducted in the submission. Refer to paragraph 7.8 for the PBAC's consideration.

Comparative effectiveness

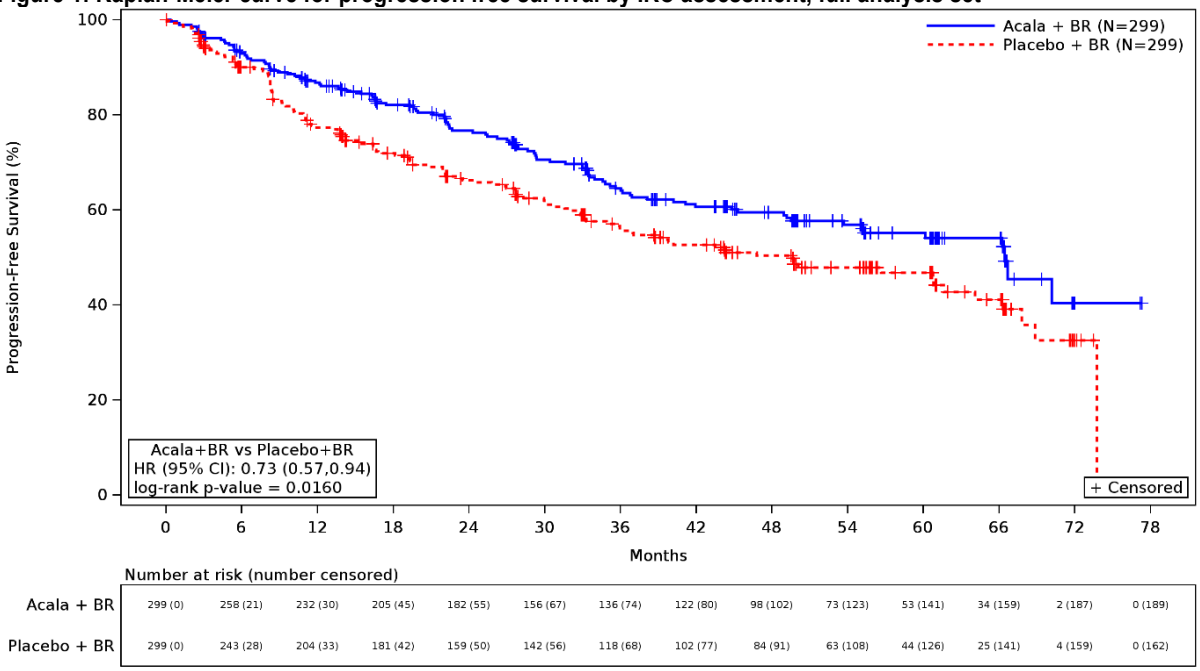
6.16 Results for the primary endpoint of the ECHO trial, progression free survival, are summarised in Table 4, with Kaplan-Meier curves for the full analysis set and for the analysis censoring for COVID-19 related deaths in Figure 1 and Figure 2.

Table 4: Progression free survival by IRC assessment, full analysis set excluding and including censoring for COVID-19 related deaths

	Full analysis set		COVID-19 censored analysis [a]	
	ABR (N = 299)	**PBR (N = 299)**	**ABR (N = 299)**	**PBR (N = 299)**
Median follow up, months (range)	46.1 (0.03, 80.10)	44.4 (0.03, 81.31)	NR	NR
Events, n (%)	110 (36.8)	137 (45.8)	83 (27.8)	117 (39.1)
Death	53 (17.7)	38 (12.7)	26 (8.7)	18 (6.0)
Disease progression	57 (19.1)	99 (33.1)	57 (19.1)	99 (33.1)
PFS (months), median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)	NE (66.4, NE)	61.6 (49.6, 68.9)
HR (95% CI), stratified analysis	**0.73 (0.57, 0.94)**		**0.64 (0.48, 0.84)**	
Kaplan-Meier estimates of progression free survival probability by timepoint (%)				
24 months (95% CI)	76.7 (71.1, 81.3)	66.2 (60.1, 71.6)	80.3 (74.9, 84.6)	69.2 (63.2, 74.4)
36 months (95% CI)	64.5 (58.1, 70.2)	56.1 (49.7, 62.0)	74.0 (68.0, 79.0)	62.1 (55.7, 67.8)
48 months (95% CI)	59.5 (52.8, 65.5)	50.4 (43.8, 56.6)	69.9 (63.5, 75.4)	57.3 (50.5, 63.5)

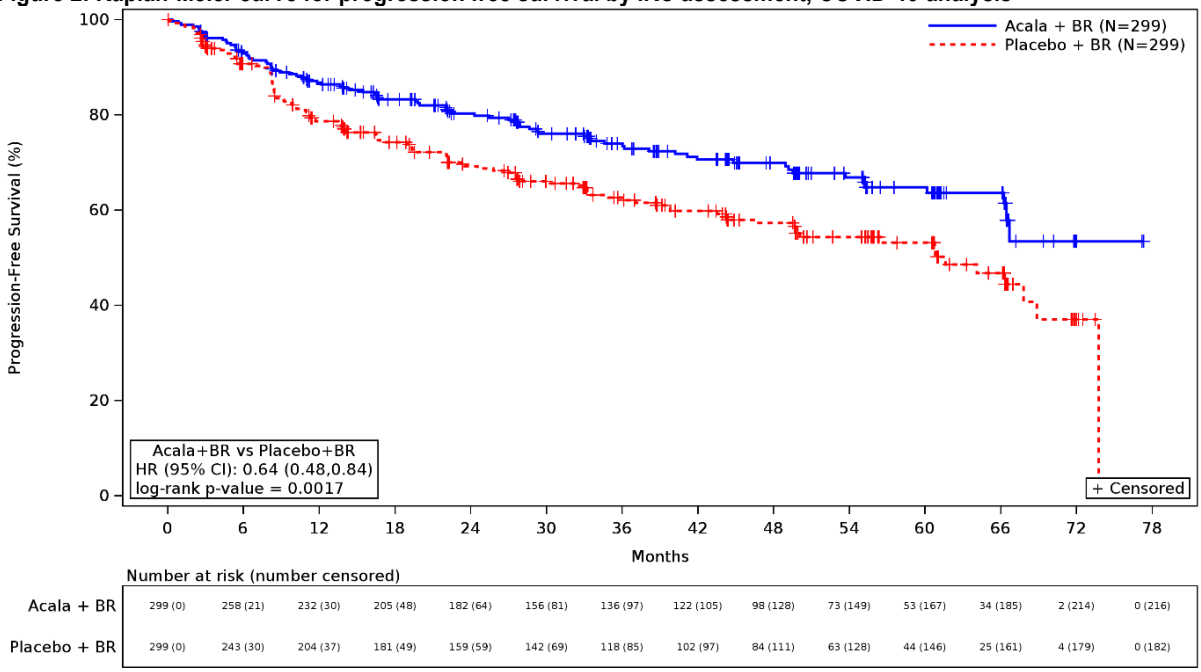
Source: Table 2-17, p56 of the submission; Table 14.1.1.3, ECHO clinical study report tables and figures.
Abbreviations; ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; HR, Hazard ratio; IRC, Independent Review Committee; NE, not estimable; PBR, placebo, bendamustine, rituximab; PFS, progression free survival
Bold indicates statistically significant results.
[a] Excluding patients with death related to COVID-19 and without progressive disease prior to death
Notes: Stratified by randomisation stratification factors: geographic region (North America, Western Europe, Other) and simplified MIPI score (low risk [0 to 3], intermediate risk [4 to 5], high risk [6 to 11])

Figure 1: Kaplan-Meier curve for progression free survival by IRC assessment, full analysis set



Source: Figure 2-5, p57 of the submission
Abbreviations: Acala, acalabrutinib; BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee

Figure 2: Kaplan-Meier curve for progression free survival by IRC assessment, COVID-19 analysis



Source: Figure 2-4, p57 of the submission
Abbreviations: Acala, acalabrutinib; BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee

6.17 Based on a median follow up of 46.1 months in the acalabrutinib arm and 44.4 months in the placebo arm and using the full analysis set, patients in the acalabrutinib arm demonstrated statistically significantly longer median progression free survival (66.4 months) compared to the placebo arm (49.6 months; HR 0.73, 95% CI 0.57, 0.94). In the COVID-19 censored analysis, a similar statistically significant difference between treatment arms was observed, with median progression free survival not reached in the acalabrutinib arm, compared to 61.6 months in the placebo arm (HR 0.64, 95% CI 0.4, 0.84). The submission argued that these results highlight the impact of deaths due to COVID-19 on the study outcomes. As discussed in paragraph 6.13, the ESC noted the uncertainty of the censored data, and considered that the data in the full analysis set was a more reasonable representation of outcomes in clinical practice.

6.18 The results of the subgroup analyses suggested that sex may be a treatment effect modifier, with a smaller treatment effect on progression free survival observed in males compared to females (males HR: 0.91; 95% CI 0.68, 1.21; females HR: 0.34; 95% CI 0.19, 0.58). In addition, the submission noted a trend towards a greater treatment effect on progression free survival in patients vaccinated against COVID-19 (HR: 0.54; 95% CI 0.35, 0.83) compared with those not vaccinated (HR: 0.95; 95% CI 0.61, 1.49; vaccination status collected when feasible). The estimated treatment effect for other subgroups generally appears consistent with the main analysis. However, the evaluation considered that the subgroup analyses should be interpreted with caution as statistical interaction testing was not conducted and the analyses may have been underpowered to detect relevant differences between subgroup populations.

6.19 Results for the key secondary endpoint of overall survival in both the full analysis set and for the analysis censoring for COVID-19 related deaths are summarised in Table 5.

Table 5: Overall survival by IRC assessment, full analysis set and censoring for COVID-19 related deaths

	Full analysis set		COVID-19 analysis [a]	
	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)
Median follow up, months (range)	46.1 (0.03, 80.10)	44.4 (0.03, 81.31)	NR	NR
Events, n (%)				
Death (all-cause)	97 (32.4)	106 (35.5)	64 (21.4)	80 (26.8)
Deaths from COVID-19	NA	NA	33 (11.0)	26 (8.7)
OS (months), median (95% CI)	NE (72.1, NE)	NE (73.8, NE)	NE (NE, NE)	NE (73.8, NE)
HR (95% CI), stratified analysis	0.86 (0.65, 1.13)		0.75 (0.53, 1.04)	
Kaplan-Meier estimates of overall survival probability by timepoint (%)				
24 months (95% CI)	83.8 (79.0, 87.6)	79.1 (73.9, 83.4)	87.0 (82.5, 90.4)	82.8 (77.8, 86.8)
36 months (95% CI)	73.8 (68.2, 78.7)	68.8 (62.9, 73.9)	83.0 (78.0, 87.0)	75.5 (69.8, 80.2)
48 months (95% CI)	68.0 (62.0, 73.3)	64.3 (58.2, 69.7)	78.8 (73.2, 83.3)	72.7 (66.8, 77.7)

Source: Table 2-18, p57 of the submission.

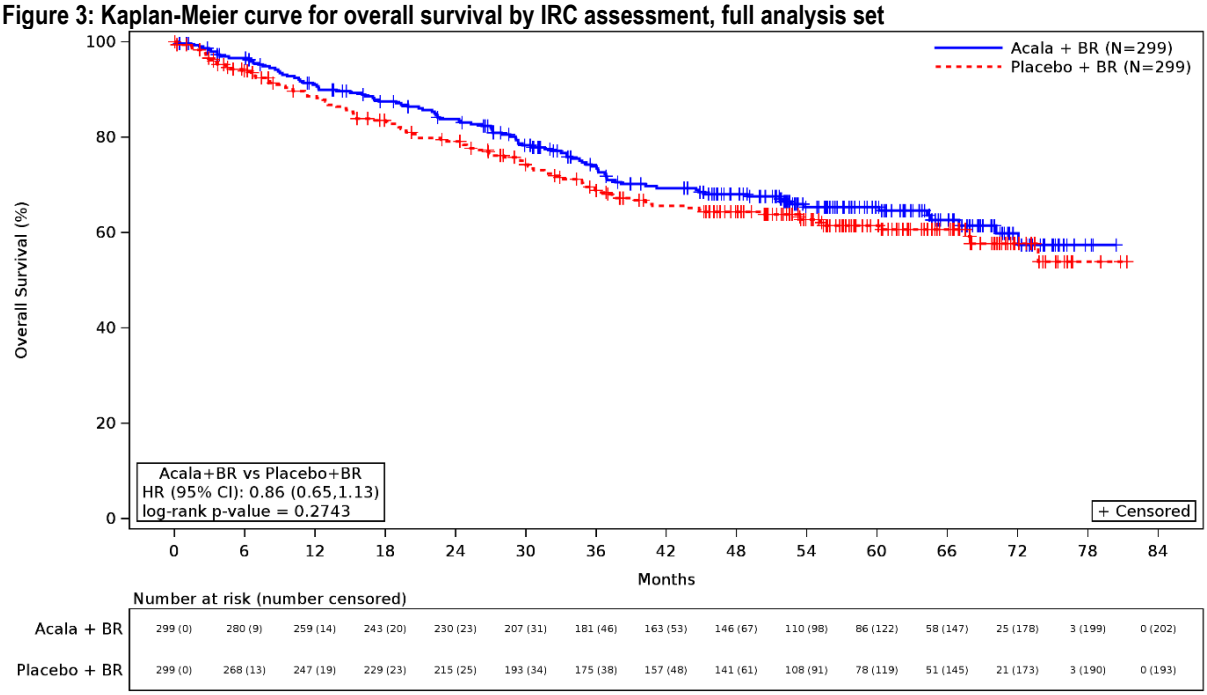
Abbreviations; ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; FAS, full analysis set; HR, Hazard ratio; IRC, Independent Review Committee; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab.

Notes: Stratified by randomisation stratification factors: geographic region (North America, Western Europe, Other) and simplified MIPI score (low risk [0 to 3], intermediate risk [4 to 5], high risk [6 to 11])

[a] Censoring COVID-19 deaths include all grade 5 Confirmed/Suspected COVID-19 infection adverse events and deaths due to a reason specified as COVID-19.

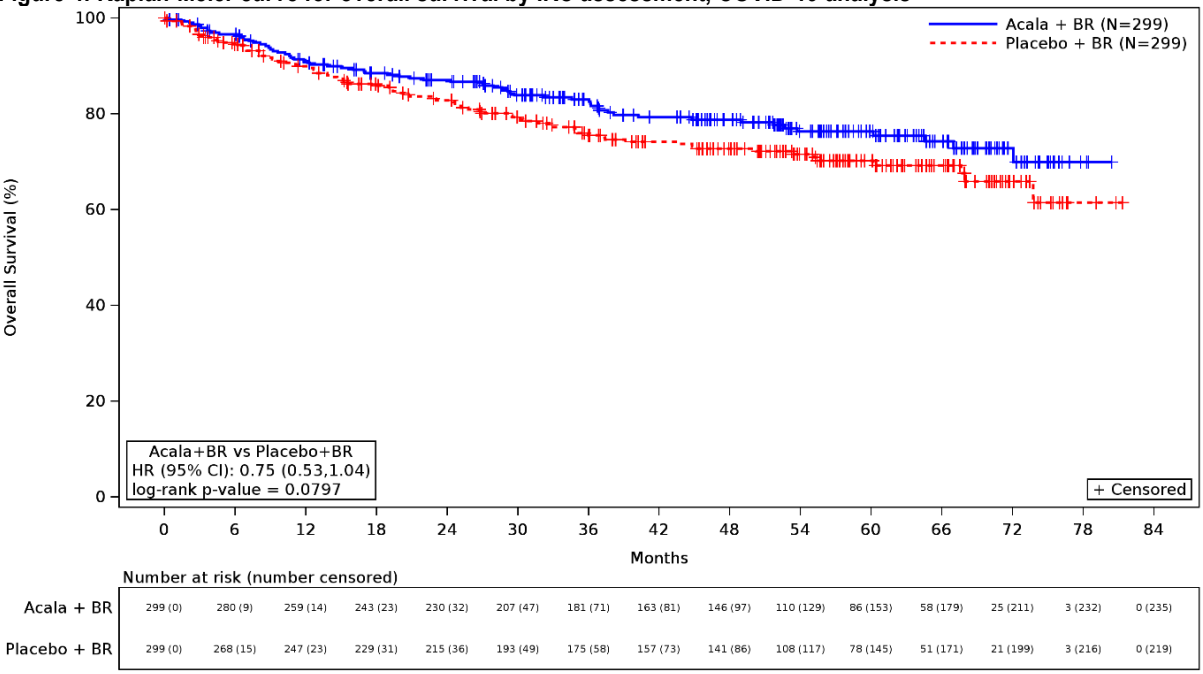
6.20 At the time of the data cut-off, 97 (32.4%) patients in the acalabrutinib arm had died, compared to 106 (35.5%) in the placebo arm, including 33 (11.0%) and 26 (8.7%) patients in the acalabrutinib and placebo arms, respectively, for whom the cause of death was confirmed or suspected to be COVID-19. Based on a median follow up of 46.1 months in the acalabrutinib arm and 44.4 months in the placebo arm, median overall survival was not reached in either treatment arm. The ESC noted that no statistically significant differences were noted between treatment arms using the full analysis set or the analysis censoring for COVID-19 related deaths, however results were more favourable towards the acalabrutinib arm in the COVID-19 censored analysis (see Figure 3 and Figure 4).

Figure 3: Kaplan-Meier curve for overall survival by IRC assessment, full analysis set



Source: Figure 2-7, p58 of the submission
Abbreviations: Acala, acalabrutinib; BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee

Figure 4: Kaplan-Meier curve for overall survival by IRC assessment, COVID-19 analysis



Source: Figure 2-6, p58 of the submission
Abbreviations: Acala, acalabrutinib; BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee

6.21 Patient reported outcomes were assessed in the ECHO trial using the Functional Assessment of Cancer Therapy-Lymphatic (FACT-Lym) scale, EQ-5D-5L index, and visual analogue scale and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) questionnaire. Summary index scores for the EQ-5D-5L were not presented, with available results presented as the proportion of patients at each score level for the 5 dimensions across treatment cycles. The submission noted that there was a general trend to improved quality of life in both treatment arms over the course of the treatment cycles, with no differences between treatment arms observed in quality of life scores.

Comparative harms

6.22 A summary of adverse events reported during the ECHO trial is presented in Table 6.

Table 6: Summary of key adverse events in the trials

Adverse Event	ABR (N = 297) n (%)	PBR (N = 297) n (%)
TEAE	296 (99.7)	294 (99.0)
Serious TEAE	205 (69.0)	184 (62.0)
Treatment-related TEAE	281 (94.6)	274 (92.3)
TEAE leading to dose withholding	242 (81.5)	207 (69.7)
TEAE leading to interrupted infusion (bendamustine and/or rituximab)	50 (16.8)	81 (27.3)
TEAE leading to decreased infusion rate (rituximab only)	7 (2.4)	6 (2.0)
TEAE leading to dose reduction (acalabrutinib/placebo and/or bendamustine)	94 (31.6)	77 (25.9)
TEAE leading to study drug discontinuation	150 (50.5)	105 (35.4)
Grade ≥3 TEAE	264 (88.9)	262 (88.2)
Deaths	97 (32.4)	106 (35.5)
Commonly reported TEAEs (≥25% in either treatment arm)		
Nausea	127 (42.8)	112 (37.7)
Neutropenia	119 (40.1)	123 (41.4)
Diarrhoea	111 (37.4)	83 (27.9)
COVID-19	91 (30.6)	62 (20.9)
Headache	90 (30.3)	42 (14.1)
Fatigue	87 (29.3)	72 (24.2)
Pyrexia	86 (29.0)	72 (24.2)
Cough	80 (26.9)	60 (20.2)
Vomiting	76 (25.6)	41 (13.8)
Constipation	73 (24.6)	75 (25.3)

Source: Table 2-24, p67; Table 2-25, p69; Table 2-26, p70; Table 2-28, p73; of the submission.
Abbreviations: ABR, acalabrutinib, bendamustine and rituximab; PBR, placebo, bendamustine and rituximab; TEAE, treatment emergent adverse event

6.23 Most patients experienced at least one adverse event (99.7% of patients in the acalabrutinib arm and 99.0% in the placebo arm), with severe adverse events reported in 88.9% and 88.2% of patients in the acalabrutinib and placebo arms, respectively. The incidences of most severe adverse events in the acalabrutinib arm were generally similar to the placebo arm, with the exception of neutrophil count decreased (15.5% and 10.1%), white blood cell count decreased (10.1% and 3.7%), COVID-19 pneumonia (13.5% and 10.4%), maculo-papular rash (7.1% and 0.7%), and febrile neutropenia

(5.1% and 2.4%), respectively. The submission stated that the incidence of some adverse events was higher in the acalabrutinib arm than the placebo arm, which was expected given the addition of acalabrutinib to the background treatment regimen, and the longer exposure to treatment in the acalabrutinib arm. The submission stated that the adverse event profile was consistent with the known safety profile of individual treatments used in each arm, including that of acalabrutinib, and of the bendamustine and rituximab regimen.

6.24 The most frequently occurring (≥5% of patients) serious adverse events reported in the acalabrutinib and placebo arms, respectively, were COVID-19 pneumonia (13.8% and 11.4%), pneumonia (9.4% and 7.1%), COVID-19 (8.8% and 6.4%), and fever (5.7% and 5.1%). Grade 3 to 4 serious adverse events in the acalabrutinib and placebo arms, respectively, were COVID-19 pneumonia (8.1% and 6.7%), pneumonia (7.1% and 6.1%), and COVID-19 (5.1% and 4.0%). Serious adverse events resulting in death included COVID-19 pneumonia (5.1% and 3.4%), COVID-19 (2.7% and 2.0%), pneumonia (1.0% and 0%), sepsis (0.3% and 0.7%) and pulmonary embolism (0 and 0.7%), in the acalabrutinib and placebo arms, respectively.

6.25 There were 97 deaths in the acalabrutinib arm and 106 in the placebo arm during the study, including the crossover period. The cause of death was adverse events in 46 (15.4%) and 41 (13.7%) patients in the acalabrutinib and placebo arms, respectively, and disease progression in 30 (10.0%) and 43 (14.4%) patients.

Benefits/harms

6.26 On the basis of direct evidence presented in the submission, over a median duration of follow-up of 45 months, for every 100 patients treated with acalabrutinib with bendamustine and rituximab compared to bendamustine and rituximab alone:

- Approximately 9 fewer patients (based on the full analysis set) or 13 fewer patients (based on the analysis censoring for COVID-19 related deaths) would experience a progression event (disease progression or death) at 4 years.
- There would be no apparent difference in deaths.
- Approximately 7 additional patients would experience a serious adverse event (mainly infections and infestations such as COVID-19 and/or pneumonia).

Clinical claim

6.27 The submission described acalabrutinib in combination with bendamustine and rituximab as superior in terms of effectiveness and inferior in terms of safety compared with placebo in combination with bendamustine and rituximab. The evaluation considered that the therapeutic conclusion presented in the submission was adequately supported by the evidence presented in the submission. However, the evaluation considered that the magnitude of benefit associated with acalabrutinib is uncertain, given:

- The clinical evidence was based on an interim analysis of the ECHO trial with immature survival data, with the final analysis expected in 2027. The PSCR considered that the median follow-up of 46.1 and 44.4 months for the acalabrutinib, and the bendamustine and rituximab arms, respectively, is sufficient to support the clinical claim. However, (as discussed in paragraph 6.17) median overall survival was not reached in either treatment arm.
- The trial allowed patients in the acalabrutinib arm to receive subsequent therapy with a BTK inhibitor (4.3% of patients in the acalabrutinib arm received a subsequent BTK inhibitor for MCL), which would not be permitted based on the current PBS listings for BTK inhibitors for relapsed/refractory MCL (see paragraph 3.5). The PSCR contended that this small proportion of patients is unlikely to introduce confounding. The ESC considered that on the PBS it is likely that a small number of patients would continue acalabrutinib post progression so long as they are obtaining clinical benefit, as there are limited options for further treatment. It was considered 4.3% would be a reasonable representation of this population. The ESC also considered that costs and outcomes should be treated consistently in the economics, and given that survival and quality of life impacts cannot be removed, it is reasonable to continue to include costs for consistency (refer to paragraph 6.43).
- The uncertain applicability to current clinical practice of the more favourable analyses with censoring of COVID-19 related deaths, particularly given causes of death are a competing risk. The ESC considered the full analysis set was a more reasonable representation of outcomes in clinical practice, however the Pre-PBAC response defended the censoring of COVID-19 related deaths (see paragraph 6.14).

6.28 The ESC considered that superior comparative effectiveness for PFS was reasonable, however OS benefit remained unclear given immature data. The ESC considered that acalabrutinib offered an improvement in patient outcomes in a relatively rare lymphoma, noting the increased risk of an adverse event.

6.29 The PBAC considered that the claim of superior comparative effectiveness was reasonable, supported by the data for the primary outcome (i.e. progression free survival).

6.30 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.31 The submission presented a stepped economic evaluation of acalabrutinib in combination with bendamustine and rituximab versus placebo in combination with bendamustine and rituximab in patients with previously untreated stage III or IV MCL. The economic evaluation was based on the results of the ECHO trial, with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-

utility analysis. The PSCR provided a revised economic model with corrected application of time to first subsequent therapy (see paragraph 6.50).

6.32 Table 7 summarises the key components of the economic evaluation.

Table 7: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Treatments	Acalabrutinib with bendamustine and rituximab versus placebo with bendamustine and rituximab
Outcomes	Progression free life years; life years; quality-adjusted life years
Time horizon	20 years in the model base case versus a mean follow-up of 41 months in the ECHO trial
Cycle length	28 days
Methods used to generate results	Partitioned survival analysis
Health states	Progression free; progressed disease; dead
Allocation to health states	The proportions of patients who were progression free, progressed and dead were informed by modelled overall survival (OS) and progression free survival (PFS) curves. PFS was further partitioned into on- and off-treatment using time on treatment (TOT) curves. Kaplan-Meier estimates for OS, PFS and TOT, censored for COVID-19 related deaths in the model base case, were derived from the ECHO trial and were used directly in the model up to 45 months (based on the median duration of follow up), then extrapolated using standard parametric functions. OS, PFS and TOT were adjusted to ensure that the risks of death, disease progression, and treatment discontinuation were not lower than the risk of general population mortality in any cycle, based on Australian life tables (ABS 2024).
Utility values	The utility associated with the progression free health state (0.830) was based on EQ-5D-5L data from the ECHO trial, cross-walked to EQ-5D-3L (UK value set) based on descriptive summary statistics for pre-progression patients in the placebo arm. Limited utility data were available for patients following disease progression in the ECHO trial. The utility associated with the progressed disease health state (0.759) was based on the utility decrement associated with progressed disease derived from the LYM-3002 trial (reported in the van Keep 2016 economic evaluation). The difference between the pre-progression and post-progression utilities of 0.071 was subtracted from the progression free health state utility of 0.830 derived from the ECHO trial. Adverse event disutilities were based on the incidence of grade 3 or higher adverse events in the ECHO trial, and selected published utility estimates from a catalogue of EQ-5D index scores based on UK preferences applied to responses to the EQ-5D questionnaire in the US-based Medical Expenditure Panel Survey (Sullivan 2011). The average adverse event disutility per patient per cycle was derived assuming patients were at risk of adverse events over 60 months.
Costs	The costs of first line treatment regimens were based on the dosage regimens in the ECHO trial, the proposed effective DPMQ of acalabrutinib and weighted DPMAs for bendamustine and rituximab, the relative dose intensity for acalabrutinib in the ECHO trial and the assumption of perfect adherence for bendamustine and rituximab, and treatment persistence informed by extrapolated time on treatment curves from the ECHO trial. The proportions of patients receiving subsequent anti-cancer treatment were informed by extrapolated time to first subsequent treatment curves from the ECHO trial. The distribution of use of first subsequent therapies was informed by use of chemotherapies and BTK inhibitors as subsequent anti-cancer therapies in the ECHO trial, and the assumption that patients who received acalabrutinib in the first line setting would not be eligible for subsequent treatment with a BTK inhibitor. Subsequent chemotherapy costs were based on alternating R-CHOP and R-DHAP dosing schedules in eviQ, weighted DPMAs, and an average duration of treatment of 3.7 months, based on the median duration of R-CHOP treatment reported in the LYM-3002 trial included in the November 2015 ibrutinib submission. Subsequent BTK inhibitor costs were based on the recommended dosage regimen of acalabrutinib for relapsed/refractory MCL in the acalabrutinib product information, the effective DPMQ for acalabrutinib for relapsed/refractory MCL, and an average duration of treatment of 17.8 months, based on the median

Component	Description
	duration of zanubrutinib treatment reported in one of 2 studies included in the July 2021 zanubrutinib submission (Study 206). Chemotherapy administration costs were based on the MBS item fee. Health state costs were based on the initial phase costs over 12 months associated with non-Hodgkin lymphoma derived from Goldsbury 2018 (based on data from the 45 and Up study), adjusted to remove PBS costs; applied to patients in the progression free and progressed disease health states over the model time horizon. Adverse event costs were based on the incidence of grade 3 or higher adverse events in the ECHO trial, and hospitalisations costs based on selected AR-DRGs (Round 24 NHCDC Cost Weights 2019-2020 Public Sector report). The average adverse event cost per patient per cycle was derived assuming patients were at risk of adverse events over 60 months.
Discounting	5% per year applied to costs and outcomes
Software package	Excel 2021

Source: Table 3-1, p89 of the submission.

6.33 The economic model utilised a partitioned survival analysis with 3 mutually exclusive health states of progression free, progressed disease, and dead, based on extrapolated progression free survival and overall survival curves over a 20 year time horizon.

6.34 The evaluation and the ESC considered that the model structure limited the ability to appropriately incorporate the costs and consequences associated with the utilisation of subsequent anti-cancer treatments. In consideration of the March and July 2015 bendamustine submissions for first-line treatment of patients with indolent non-Hodgkin lymphoma or MCL, based on a 3 health state Markov model, the PBAC considered that the model should incorporate the impact of further lines of treatment with their costs and health benefits (para 7.15, bendamustine Public Summary Document (PSD), March 2015 PBAC meeting). The PBAC also previously noted the inherent disconnect between using both a 3 health state model and a 20 year time horizon that does not account for different health states over time (para 7.7, bendamustine PSD, July 2015 PBAC meeting). The PBAC previously considered that a 10 year time horizon should be used for the first-line MCL bendamustine submission (para 7.15, bendamustine PSD, March 2015 PBAC meeting). The ESC considered that a 20 year time horizon would be optimistic and that a 10 year time horizon would be more appropriate.

6.35 The PSCR and Pre-PBAC response argued that the 3 health state model incorporated subsequent lines of treatment in accordance with the clinical trial. However, the ESC noted that the model only incorporated the first subsequent treatment, based on data from the ECHO trial (i.e. it did not include additional lines of therapy after second line) and was based on a mean duration of follow-up in the trial of 41 months, which was extrapolated to 20 years. Further, the ESC considered the model did not allow the costs and treatment effects of subsequent lines of therapies to be considered at a more granular level.

6.36 The extrapolation of overall survival curves resulted in a survival benefit for acalabrutinib compared with placebo that was not demonstrated in the ECHO trial.

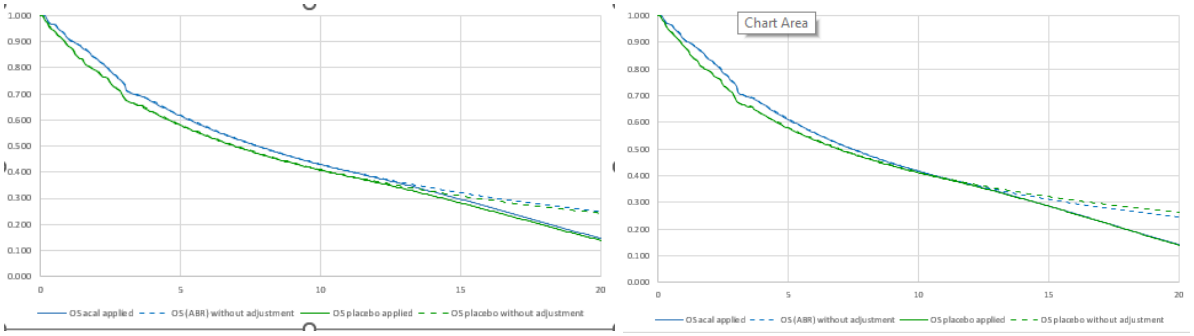
6.37 The submission did not consider the face validity of the extrapolated overall survival curves used in the partitioned survival analysis, with most parametric functions, including the selected OS distributions, overestimating 20 year survival compared to the Australian general population. As a consequence, the overall survival curves were subsequently adjusted to ensure that the risk of death in any cycle was not lower than the risk of general population mortality in any cycle, based on Australian life tables. The ESC noted that most of the standard parametric functions required this adjustment and considered that the need for adjustment suggests the 3 health state model (partitioned survival analysis with parametric functions) may not be accurately capturing long-term survival in this condition (i.e. only 12.7% of patients in the placebo arm of the trial had died at the time of data cut-off, and the death rates over the trial follow-up period may not be reflective of the long term mortality with this condition). The ESC considered that, in this context, overall survival extrapolations that produce smaller gains in life years (e.g. application of the log-logistic function in the model uncensored for COVID deaths) reduced the extent of uncertainty.

6.38 The Pre-PBAC response stated that the impact of any potential disconnect between a 3 health state trial-based analysis and a twenty-year time horizon was minimal due to the relatively slow progression of MCL, and the age of the population (average 71.6 years in ECHO) i.e., as patients age, risks of death from non-cancer causes become increasingly relevant. The response further contended that incorporation of all-cause mortality was necessary as not all patients ultimately die from MCL, and thus parametric functions based on the trial data are not able to accurately predict the increasing background mortality with age. The response argued that the submission's approach only applied the maximum of the risks of death from general population mortality versus the parametric function (and thus acalabrutinib was not associated with a survival advantage versus BSC once the general population mortality risks exceed the parametric function risks) rather than an additive approach. The Pre-PBAC response stated that 'by applying the same risk of death in each arm of the model, this approach resolves any potential disconnect'.

6.39 Overall, the PBAC noted that many patients with MCL survive beyond 10 years but considered that a 10-year time horizon would be more appropriate given the uncertain OS outcomes and limitations of the model structure which meant the extrapolation of OS beyond 10 years was unreliable.

6.40 The ESC noted that for the full analysis set without censoring for COVID-19 related deaths, overall survival was extrapolated using the generalised gamma function (whereas the lognormal function was used for the COVID-censored analysis), with no justification provided in the submission. For the full analysis set (without censoring for COVID-19 related deaths), the generalised gamma function was one of the poorer fitting functions, with the log-logistic being better fitting based on AIC and BIC, which increased the ICER by [redacted]% (in the PSCR full analysis set model). Figure 5 shows the overall survival extrapolations with the lognormal and log-logistic functions (the dotted lines represent extrapolated survival before applying the adjustment for the risk of all-cause mortality, the solid lines represent the survival applied in the model).

Figure 5: Overall survival using the full analysis set without censoring for COVID-19 related deaths (using the lognormal (left) and log-logistic (right) functions (dotted lines are without adjustment for all-cause mortality)



Source: Developed during preparation of ESC Advice

6.41 Progression free survival and time on treatment curves were also adjusted to ensure that the risks of disease progression and treatment discontinuation were not lower than the risk of general population mortality in each cycle.

6.42 In the submission, the proportions of patients initiating subsequent anti-cancer therapy over time were based on 'time to first subsequent therapy or death' rather than 'time to first subsequent therapy censored for all-cause death', which was claimed in the submission. The difference resulted in an overestimation of the proportion of patients initiating subsequent therapies in the model compared to the observed data from the trial, due to the inclusion of deaths as a subsequent treatment event. The PSCR acknowledged that the incorrect time to first subsequent therapy curves were applied in the economic model, and provided a corrected economic model with time to first subsequent therapy appropriately censored for death.

6.43 The distribution of subsequent anti-cancer therapies in the placebo arm was based on the first subsequent therapies initiated in the ECHO trial (BTK inhibitors, chemotherapy), adjusted for therapies considered not relevant or available in Australia. It was assumed that all patients who received subsequent therapy in the acalabrutinib arm would receive chemotherapy, based on the one per lifetime rule for BTK inhibitors (discussed in paragraph 3.5). However, as discussed in paragraph 6.27, a proportion (4.3%) of patients in the acalabrutinib arm of the ECHO trial received subsequent BTK inhibitor. Although the costs of subsequent BTK therapy were removed from the acalabrutinib arm of the model, the submission assumed that this would have no impact on the disease trajectory, despite potential impacts on both survival and quality of life. The PSCR argued that these patients, who had recently relapsed on first-line BTK inhibitors, were unlikely to benefit from BTK inhibitor re-treatment and thus the impact of this assumption on survival endpoints was expected to be minimal. However, the ESC considered that costs and outcomes should be treated consistently, and given that survival and quality of life impacts cannot be removed, it was reasonable to continue to include costs for consistency. As discussed in paragraphs 6.27 and 3.5, the ESC considered the proportion observed in the ECHO trial (4.3%) was a reasonable representation of the proportion of patients who may continue to use acalabrutinib post-progression in clinical practice.

6.44 The utility associated with the progression free health state (0.830) was based on EQ-5D-5L data from the ECHO trial, cross-walked to EQ-5D-3L (UK value set). The submission acknowledged that Australian value sets were available, but claimed that direct application of the EQ-5D-5L Australian value set resulted in utility values for the progression free and progressed disease health states that exceeded 0.9, which the submission considered to be implausible given these were higher than the utility of the general Australian population aged above 71 years old. The submission stated that, as a result, mapped utility values from the UK were considered the best alternative. Limited utility data were available for patients following disease progression in the ECHO trial. Thus, the utility associated with the progressed disease health state (0.759) was based on the utility decrement associated with progressed disease derived from the LYM-3002 trial (reported in the van Keep 2016 economic evaluation). The difference between the pre-progression and post-progression utilities of 0.071 was subtracted from the progression free health state utility of 0.830 derived from the ECHO trial. The ESC considered that the validity of the utility applied for the progression-free health state was unclear (given it was based on trial data that appeared to overestimate quality of life when the Australian value sets were applied), and noted that a sensitivity analysis using the values from van Keep 2016 for both health states (0.764 and 0.693 for the progression free and progressed disease health states, respectively) increased the ICER by [redacted]%.

6.45 The submission's base case results of the economic evaluation were based on the analysis censoring for COVID-19 related deaths, given the impact of the COVID-19 pandemic on study outcomes, which results in more favourable outcomes for acalabrutinib versus placebo, given the higher proportion of COVID-related deaths in the acalabrutinib arm (see paragraphs 6.14 and 6.27). The evaluation considered that this may be the result of acalabrutinib patients being at greater risk of infection, with greater immunosuppression associated with ongoing use of acalabrutinib; to which the PSCR agreed. The evaluation considered it was unclear whether the analyses censored for COVID-19 related deaths would be representative of outcomes in current clinical practice, given causes of death are a competing risk. As discussed in paragraph 6.14, the PSCR argued that the COVID-censored analysis was appropriate, however the ESC considered that the full analysis set should be used for both the clinical and economic evaluations, as the analysis censoring for COVID-19 related deaths does not account for competing causes of death, and favours acalabrutinib.

6.46 Key drivers of the economic model are summarised in Table 8.

Table 8: Key drivers of the model

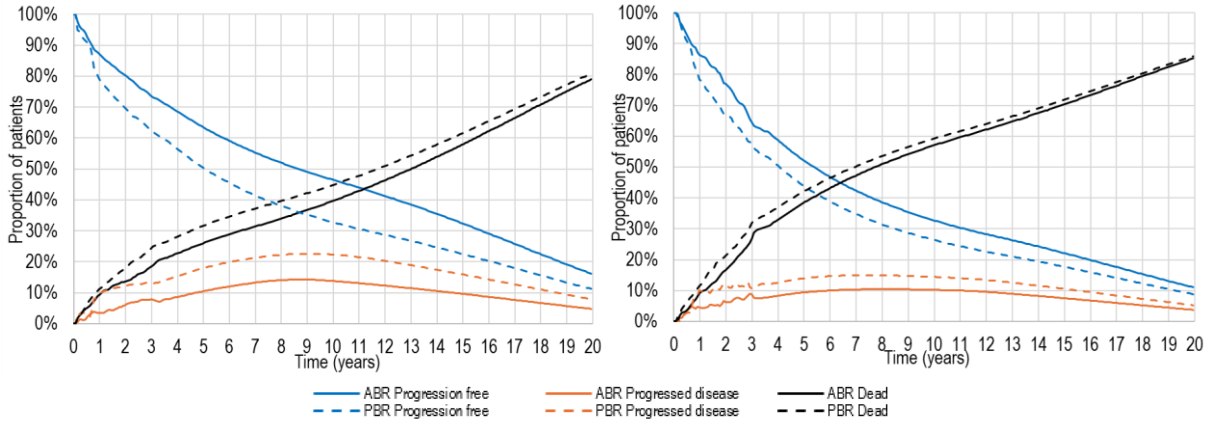
Description	Method/Value	Impact
Model structure	The evaluation and the ESC considered that the 3 health state partitioned survival analysis limited the ability to appropriately incorporate the costs and consequences associated with the utilisation of subsequent anti-cancer treatments over the 20 year model time horizon. The PBAC has previously noted its strong preference to incorporate the impact of further lines of treatment, with their costs and health benefits, to enable robust assessments of cost-effectiveness (para 7.15, bendamustine PSD, March 2015 PBAC meeting; para 7.4, bendamustine PSD, July 2015 PBAC meeting). The PBAC also noted the inherent disconnect between using both a 3 health state model and a 20 year model time horizon, and considered a 10 year time horizon should be used for first-line MCL (para 7.7, bendamustine PSD, July 2015 PBAC meeting; para 7.15, bendamustine PSD, March 2015 PBAC meeting). Similarly, the ESC considered that a 20 year time horizon is optimistic for this submission and a 10 year horizon would be more feasible. However, the submission's model was relatively insensitive to the time horizon particularly in the uncensored full analysis set (FAS) scenario, where the ICER increased by only [redacted]% when the time horizon was shortened from 20 years to 10 years. The ESC considered that reasons for this include the small difference in OS beyond 10 years (particularly in the FAS where more patients in the acalabrutinib arm die early due to COVID-19), with most patients in the progression free health state continuing to receive acalabrutinib and thus accruing drug costs with longer time horizons. The ESC also noted that in the sensitivity analysis where the OS extrapolation is more conservative (i.e. log-log and log-normal), shorter time horizons reduce the ICER.	Unclear (with the impact not adequately assessed by simply truncating the time horizon)
Subsequent anti-cancer therapy	The submission assumed that all patients who received subsequent anti-cancer therapy in the acalabrutinib arm received chemotherapy. This was inconsistent with the ECHO trial, in which a proportion of patients in the acalabrutinib arm (4.3%) received subsequent BTK inhibitor therapy. This was implemented as a reduction in the modelled costs of subsequent anti-cancer therapies in the acalabrutinib arm, without corresponding changes to the modelled survival endpoints or quality of life.	Moderate, favours acalabrutinib (impact is lesser in the PSCR model compared with the submission model)
Use of the analysis censoring for COVID-19 related deaths	The use of the analyses censoring for COVID-19 related deaths in the model base case was not conservative, given the higher proportion of COVID-related deaths in the acalabrutinib arm compared to the placebo arm, and uncertainty regarding whether the results would be representative of outcomes in current clinical practice, given causes of death are a competing risk. The ESC considered that the full analysis set should be used.	High, favours acalabrutinib

Source: Constructed during the evaluation

Abbreviations: BTK, Bruton tyrosine kinase; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public summary Document.

6.47 Figure 6 presents the model traces for the acalabrutinib and placebo arms of the economic model, with and without censoring for COVID-19 related deaths.

Figure 6: Model traces for the acalabrutinib and placebo arms: FAS censoring for COVID-19 related deaths (left) and FAS (right)



Source: '3.1 ACAL_Section3model_March2025' model spreadsheet provided with the submission.
Abbreviations: ABR, acalabrutinib with bendamustine and rituximab; PBR, placebo with bendamustine and rituximab

6.48 The model traces show a modelled survival benefit for acalabrutinib compared to placebo that persists over the 20 year model duration. The modelled survival benefit for acalabrutinib was inconsistent with the results of the ECHO trial, which did not demonstrate a statistically significant difference in overall survival between acalabrutinib and placebo. The traces also show a larger proportion of patients remaining progression free in the acalabrutinib arm compared to the placebo arm, which persists over the modelled time horizon. Similarly, smaller proportions of patients were in the progressed disease state in the acalabrutinib arm compared to the placebo arm.

6.49 The model traces for the full analysis set (uncensored for COVID-19 related deaths) show smaller modelled benefits for acalabrutinib versus placebo compared to the model trace censoring for COVID-19 related deaths.

6.50 In the ECHO trial, over a mean duration of follow-up of 41 months (3.42 years), 10.0% of patients in the acalabrutinib arm and 29.4% of patients in the placebo arm initiated subsequent anti-cancer therapy. The submission's model appeared to overestimate the proportion of patients receiving subsequent anti-cancer therapy, likely due to the use of time to first subsequent therapy curves that included deaths as an outcome, which favoured acalabrutinib due to the higher costs associated with subsequent therapy in the placebo arm associated with BTK inhibitor use ($53,093 versus $9,123 in the acalabrutinib arm). The PSCR's model applied time to first subsequent therapy censored for death, which better aligned the modelled proportions of patients using subsequent anticancer therapy with the proportions in the ECHO trial (10.0% and 29.4% at a median follow-up of 3.42 years). This reduced the subsequent treatment costs in both arms, and reduced the incremental offsets (savings) for subsequent treatments from $24,494 in the submission to $20,433 in the PSCR (discounted). Estimates of the cumulative incidence of initiation of subsequent anti-cancer therapy in the PSCR economic model are shown in Table 9.

Table 9: Comparison of modelled cumulative incidence of subsequent anti-cancer therapy with proportions of patients initiating at least one anti-cancer therapy in the ECHO trial (PSCR model)

	Modelled cumulative incidence subsequent anti-cancer therapy				Patients with at ≥1 subsequent therapy in the ECHO trial[a]	
	FAS censored for COVID-19 related deaths		FAS (not censored for COVID)			
	ABR	PBR	ABR	PBR	ABR	PBR
1 year	3.3%	13.5%	3.3%	13.5%	10.0% (at mean follow-up of 3.42 years)	29.4% (at mean follow-up of 3.42 years)
2 years	5.9%	19.7%	5.9%	19.6%		
3 years	7.8%	24.0%	7.7%	23.6%		
4 years	9.5%	27.4%	9.2%	26.6%		
5 years	11.5%	31.5%	10.9%	30.1%		
6 years	13.2%	34.8%	12.3%	32.8%		

Source: Constructed during preparation of the ESC Advice based on the economic model spreadsheet provided with the PSCR.
Abbreviations: ABR, acalabrutinib with bendamustine and rituximab; FAS, full analysis set; PBR, placebo with bendamustine and rituximab.
[a] Based on a mean follow-up of 41 months (3.42 years)

6.51 Table 10 presents the results of the model base case provided in the submission and also the revised model presented with PSCR, based on overall survival, progression free survival, and time on treatment curves with and without censoring for COVID-19 related deaths.

Table 10: Results of the economic evaluation

	Acalabrutinib + BR	Placebo + BR	Increment
Submission base case: FAS with censoring for COVID-19 related deaths			
Costs	$[redacted]	$63,387	$[redacted]
QALYs	6.8891	6.3623	0.5268
Incremental cost per QALY gained			**$[redacted][1]**
PSCR: FAS with censoring for COVID-19 related deaths and corrected for time to subsequent treatment curves [a]			
Costs	$[redacted]	$56,735	$[redacted]
QALYs	6.89	6.36	0.527
Incremental cost per QALY gained			**$[redacted][1]**
FAS (without censoring for COVID-19 related deaths)			
Costs	$[redacted]	$58,072	$[redacted]
QALYs	5.7263	5.4065	0.3197
Incremental cost per QALY gained			**$[redacted][2]**
PSCR: FAS without censoring for COVID-19 related deaths and corrected for time to subsequent treatment curves [a]			
Costs	$[redacted]	$51,433	$[redacted]
QALYs	5.73	5.41	0.320
Incremental cost per QALY gained			**$[redacted][3]**

Source: Table 3-29, p141 of the submission; '3.1 ACAL_Section3model_March2025' model spreadsheet provided with the submission.
Abbreviations: BR, bendamustine and rituximab; FAS, full analysis set; QALY, quality adjusted life year
[a] added during preparation of the ESC Advice based on the economic model spreadsheet provided with the PSCR.
The redacted values *correspond to the following ranges:*
[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*
[3] *$95,000 to < $115,000*

6.52 Based on the submission's economic model, treatment with acalabrutinib plus bendamustine and rituximab compared to bendamustine and rituximab alone was associated with an incremental cost per QALY gained of $55,000 to < $75,000 using the full analysis set with censoring for COVID-19 related deaths, and an incremental cost per QALY gained of $75,000 to < $95,000 based on the full analysis set without censoring for COVID-19 related deaths. The PSCR corrected model resulted in ICERs of $55,000 to < $75,000 and $95,000 to < $115,000 per QALY for the COVID-19 censored

and uncensored analyses, respectively (i.e. increased the ICER by [redacted]% and [redacted]%, respectively, compared with the submission base case).

6.53 The submission stated that the base case ICER of $55,000 to < $75,000 per QALY gained is consistent with previous PBAC decision making for first line non-Hodgkin lymphoma, with the July 2020 submission for venetoclax in combination with obinutuzumab for previously untreated chronic lymphocytic leukaemia recommended with an ICER of between $55,000 to < $75,000 and $75,000 to < $95,000 per QALY gained. However, as part of that previous consideration, the PBAC had noted that the ICER was not less than $45,000 to < $55,000 per QALY gained as previously requested, but accepted the sponsor's arguments regarding aspects of the modelling being potentially conservative; and considered that the fixed 12 month treatment duration of venetoclax mitigated some of the uncertainty regarding the treatment costs per patient (para 6.8, venetoclax PSD, July 2020 PBAC meeting).

6.54 The evaluation noted that the PBAC has previously accepted an ICER of between $15,000 to < $25,000 and $45,000 to < $55,000 per QALY gained for bendamustine in combination with rituximab in previously untreated MCL. While the PBAC remained concerned about the limitations of the 3 health state model and application of a 20 year time horizon, these concerns were diminished given projected cost savings to the Commonwealth (para 7.8, bendamustine PSD, July 2015 PBAC meeting).

6.55 The acalabrutinib model uses the same model structure and time horizon that the PBAC was concerned about during its consideration of bendamustine. Unlike bendamustine plus rituximab (maximum treatment duration 24 weeks) and venetoclax plus obinutuzumab (maximum treatment duration 12 months), acalabrutinib treatment in the previously-untreated MCL setting is ongoing until disease progression or unacceptable toxicity; and a number of assumptions used in the economic model were not conservative (selection of the analysis censoring for COVID-19 related deaths; and excluding the costs but not the benefits of BTK inhibitor therapy as subsequent therapy in the acalabrutinib arm).

6.56 For every patient treated with acalabrutinib versus placebo (both in combination with bendamustine and rituximab) and followed up for 20 years, the submission's economic evaluation based on the full analysis set with censoring for COVID-19 related deaths (without discounting) estimated that there would be:

- Additional initial treatment costs of $[redacted], additional disease management costs of $1,796, and additional adverse event management costs of $783.
- Reduced costs of subsequent therapies of $24,292.
- An additional 2.14 years of progression free survival, 0.84 years of overall survival and 0.79 quality adjusted life years.

6.57 For every patient treated with acalabrutinib versus placebo (both in combination with bendamustine and rituximab) and followed up for 20 years, the submission's economic evaluation based on the full analysis set (without discounting) estimated that there would be:

- Additional initial treatment costs of $[redacted], additional disease management costs of $1,006, and additional adverse event management costs of $363.
- Reduced costs of subsequent therapies of $21,691.
- An additional 1.18 years of progression free survival, 0.47 years of overall survival and 0.44 quality adjusted life years.

6.58 The results of key sensitivity analyses are summarised in Table 11, based on the full analysis set with and without censoring for COVID-19 related deaths, using the PSCR model.

Table 11: Results of key sensitivity analyses based on the PSCR model

Analysis	Censored for COVID-19 related deaths		Full analysis set (without censoring for COVID)	
	ICER	% change	ICER	% change
Base case – submission	**$[redacted]** [1]		**$[redacted]** [2]	
Base case – PSCR	**$[redacted]** [1]		**$[redacted]** [3]	
Discount rate (base case: 5% costs and outcomes)				
0%	$[redacted] [1]	-[redacted]%	$[redacted] [3]	-[redacted]%
3.5%	$[redacted] [1]	-[redacted]%	$[redacted] [3]	-[redacted]%
Time horizon (base case: 20 years)				
#A 10 years	$[redacted] [2]	[redacted]%	$[redacted] [3]	[redacted]%
15 years	$[redacted] [2]	[redacted]%	$[redacted] [3]	[redacted]%
25 years	$[redacted] [1]	-[redacted]%	$[redacted] [3]	[redacted]%
Extrapolation of survival curves (base case: Kaplan-Meier data used for 45 months, based on median follow-up of the ECHO trial)				
Extrapolation of KM curves from 50 months	$[redacted] [1]	-[redacted]%	$[redacted] [3]	-[redacted]%
Extrapolation of KM curves from 55 months	$[redacted] [2]	[redacted]%	$[redacted] [4]	[redacted]%
Extrapolation of KM curves from 60 months	$[redacted] [2]	[redacted]%	$[redacted] [3]	-[redacted]%
Overall survival (OS) extrapolation (base case: log-normal function for COVID- censored and gen-gamma for FAS)				
OS extrapolated using an exponential function	$[redacted] [7]	-[redacted]%	$[redacted] [1]	-[redacted]%
OS extrapolated using a Gompertz function	$[redacted] [1]	-[redacted]%	$[redacted] [5]	[redacted]%
#B OS extrapolated using a log-logistic function	$[redacted] [1]	-[redacted]%	$[redacted] [4]	[redacted]%
OS extrapolated using a Weibull function	$[redacted] [8]	-[redacted]%	$[redacted] [6]	-[redacted]%
OS extrapolated using a gamma function	$[redacted] [1]	-[redacted]%	-	-
OS extrapolated using a log-normal function	-	-	$[redacted] [4]	[redacted]%
Progression free survival (PFS) extrapolation (base case: log-logistic function)				
PFS extrapolated using an exponential function	$[redacted] [1]	-[redacted]%	$[redacted] [3]	-[redacted]%
PFS extrapolated using a Gompertz function	$[redacted] [1]	-[redacted]%	$[redacted] [4]	[redacted]%
PFS extrapolated using a Weibull function	$[redacted] [1]	[redacted]%	$[redacted] [2]	-[redacted]%
PFS extrapolated using a lognormal function	$[redacted] [1]	[redacted]%	$[redacted] [3]	-[redacted]%
PFS extrapolated using a gamma function	$[redacted] [1]	-[redacted]%	$[redacted] [3]	-[redacted]%
Time on (initial) treatment (TOT) extrapolation (base case: log-logistic function)				
TOT extrapolated using an exponential function	$[redacted] [7]	-[redacted]%	$[redacted] [1]	-[redacted]%
TOT extrapolated using a Gompertz function	$[redacted] [2]	[redacted]%	$[redacted] [3]	[redacted]%
TOT extrapolated using a Weibull function	$[redacted] [6]	-[redacted]%	$[redacted] [7]	-[redacted]%
TOT extrapolated using a lognormal function	$[redacted] [2]	[redacted]%	$[redacted] [3]	[redacted]%
TOT extrapolated using a gamma function	$[redacted] [1]	-[redacted]%	$[redacted] [2]	-[redacted]%
Time to first subsequent treatment (TFST) extrapolation (base case: log-logistic function applied to time to initiation of first subsequent therapy or death)				
TFST extrapolated using an exponential function	$[redacted] [1]	-[redacted]%	$[redacted] [2]	-[redacted]%
TFST extrapolated using a Gompertz function	$[redacted] [2]	[redacted]%	$[redacted] [3]	[redacted]%
TFST extrapolated using a Weibull function	$[redacted] [1]	-[redacted]%	$[redacted] [2]	-[redacted]%

Analysis	Censored for COVID-19 related deaths		Full analysis set (without censoring for COVID)	
	ICER	% change	ICER	% change
Base case – submission	$[redacted][1]		$[redacted][2]	
Base case – PSCR	$[redacted][1]		$[redacted][3]	
TFST extrapolated using a lognormal function	$[redacted][1]	[redacted]%	$[redacted][3]	[redacted]%
TFST extrapolated using a gamma function	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
Health state utilities (base case: progression free utility (0.830) based on ECHO trial; progressed disease utility (0.759) derived from van Keep 2016)				
#C van Keep health state utilities (progression free 0.764; progressed disease 0.693)	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
Average adverse event disutility and cost per cycle (base case: weighted average costs and disutilities per patient per treatment arm divided by 60 months to derive an average cost per cycle)				
Average adverse event disutility and cost per cycle derived based on mean duration of treatment (ABR 32.461 months; PBR 29.121 months)	$[redacted][1]	[redacted]%	$[redacted][3]	[redacted]%
Subsequent therapy costs (base case: patients in the acalabrutinib arm who received subsequent BTK inhibitor therapy assumed to receive chemotherapy; duration of subsequent BTK inhibitor therapy in placebo arm 17.8 months at a cost of $63,144; duration of chemotherapy 3.7 months at a cost of $9,123)				
#D Use of BTK inhibitors as first subsequent therapy for the acalabrutinib arm, consistent with ECHO trial[a]	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
Duration of subsequent BTK inhibitor therapy 15 months	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
Duration of subsequent BTK inhibitor therapy 20 months	$[redacted][1]	-[redacted]%	$[redacted][2]	-[redacted]%
Costs of subsequent chemotherapy doubled	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
Costs of subsequent chemotherapy halved	$[redacted][1]	-[redacted]%	$[redacted][3]	-[redacted]%
Multivariate sensitivity analyses				
#A + #B (10 year time horizon + OS log-logistic)	$[redacted][2]	[redacted]%	$[redacted][4]	[redacted]%
#A + #B + #D (10 year time horizon + OS log-logistic + BTKi use in acalabrutinib arm as per ECHO)	$[redacted][2]	[redacted]%	$[redacted][4]	[redacted]%
#A + #D (10 year time horizon + BTKi use in acalabrutinib arm as per ECHO)	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
#B + #D (OS log-logistic + BTKi use in acalabrutinib arm as per ECHO)	$[redacted][1]	[redacted]%	$[redacted][9]	[redacted]%
# A+ #B + #C + #D (10 year time horizon + OS log-logistic + van Keep utilities + BTKi use in acalabrutinib arm as per ECHO)	$[redacted][2]	[redacted]%	$[redacted][9]	[redacted]%

Source: Table 3-33, p145 of the submission; '3.1 ACAL_Section3model_March2025' model spreadsheet provided with the submission.
Abbreviations: ABR, acalabrutinib with bendamustine and rituximab; BR, bendamustine and rituximab; BTK, Bruton tyrosine kinase; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; N/A, not applicable; OS, overall survival; PBR, placebo with bendamustine and rituximab; PFS, progression free survival; QALY, quality adjusted life year; TFST, time to first subsequent therapy; TOT, time on (initial) therapy.

[a] 10 patients in the acalabrutinib arm received a BTK inhibitor as initial subsequent therapy out of 23 patients who received a BTK inhibitor or chemotherapy (excluding therapies considered not relevant or available in Australia).

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*
[3] *$95,000 to < $115,000*
[4] *$115,000 to < $135,000*
[5] *$355,000 to < $455,000*
[6] *$25,000 to < $35,000*
[7] *$45,000 to < $55,000*
[8] *$35,000 to < $45,000*

[9] *$135,000 to < $155,000*

6.59 The economic model was most sensitive to the parametric functions used to extrapolate overall survival and time on initial treatment, the inclusion of the costs of BTK inhibitors as first subsequent therapy for the acalabrutinib arm (consistent with clinical outcomes from the ECHO trial), and the duration of subsequent BTK inhibitor therapy. Due to the partitioned survival design, changes to subsequent treatments only affected modelled costs without affecting the modelled survival endpoints or quality of life. The ESC noted that sensitivity analyses on the point of extrapolation had only a minor impact, and considered that 45 months was not unreasonable.

6.60 The ESC considered that the following multivariate sensitivity analysis was informative: full analysis set without censoring for COVID-19 related deaths (and corrected time to subsequent treatment curves as per PSCR); log-logistic extrapolation of overall survival; and costs of BTK inhibitors in the acalabrutinib arm consistent with the trial, noting this increased the ICER to $135,000 to < $155,000 per QALY. The ESC considered the multivariate sensitivity analyses using the van Keep utilities was also informative and could reflect a respecified base case. Refer to paragraphs 7.11 to 7.13 for the PBAC's consideration.

6.61 The ESC also noted that in its March 2018 recommendation of ibrutinib for relapsed/refractory MCL, the PBAC advised that an RSA was necessary to achieve cost-effectiveness i.e. the PSD states 'The PBAC noted that this price was lower than the requested effective DPMQ on the basis that the difference would be rebated through the RSA' and that the ICER was reduced due to the assumption that [redacted]% of Commonwealth expenditure on ibrutinib would be rebated through the RSA' (paragraphs 12.1 and 6.8, ibrutinib PSD, March 2018 PBAC meeting).

Drug cost/patient/year

Table 12: Drug cost per patient per year for acalabrutinib based on the submission's base case

	ECHO trial	Economic model	Financial estimates
Daily dose	100 mg twice daily	100 mg twice daily	100 mg twice daily
Mean duration of treatment	32.461 months	73.94 months	73.73 months
Adherence[a]	89.08%	89.08%	89.02%
Number of scripts per year[b]	-	11.62	11.61
Cost per pack of 56 100 mg tablets (proposed effective DPMQ)	-	$[redacted]	$[redacted]
Cost per year	-	$[redacted]	$[redacted]
Proportion of patients on treatment (persistence)[c]	Year 1: 73.1% Year 2: 57.9% Year 3: 43.2% Year 4: 37.4% Year 5: 32.5% Year 6: 24.9%	Year 1: 72.8% Year 2: 61.1% Year 3: 49.0% Year 4: 44.1% Year 5: 38.8% Year 6: 34.7%	Year 1: 100% Year 2: 100% Year 3: 100% Year 4: 100% Year 5: 100% Year 6: 100%
Average cost per patient	-	COVID-censored analysis: $[redacted] over 6 years $[redacted] over 20 years[d] FAS (uncensored): $[redacted] over 6 years; $[redacted] over 20 years	$[redacted] over 6 years

Source: Constructed during the evaluation based on the ECHO trial CSR, '3.1 ACAL_Section3model_March2025' model spreadsheet and '4.2 Acala UCM March 2025' budget impact spreadsheet provided with the submission.

[a] Relative dose intensity for acalabrutinib in the ECHO trial

[b] Calculated as the estimated number of scripts required per year (365.25/28) adjusted for treatment adherence.

[c] Based on the proportion of patients on treatment at the end of each year. For the ECHO trial, based on Kaplan-Meier data for the ECHO trial in the 'Curves_RawKM' worksheet of the 'ACAL_Section3model_March2025' Excel workbook for the full analysis set (without censoring for COVID-19 related deaths). For the economic model, based on the proportion of patients in the progression free on treatment health state in the 'MarkovTrace_ABR' worksheet of the 'ACAL_Section3model_March2025' Excel workbook for the model base case (with censoring for COVID-19 related deaths). For the financial estimates, all patients assumed to receive 73.73 months of acalabrutinib treatment (100% adherence over more than 6 years).

[d] 8.4% of patients remain on acalabrutinib treatment after 20 years in the economic model. Average duration of treatment in the economic model, COVID-censored analysis, was 6.1 years (undiscounted, over the base case 20 year time horizon). When the time horizon was shortened to 6 years, to align with the financial estimates, the average duration of treatment was 3.3 years (undiscounted). These are undiscounted costs.

6.62 The drug cost per patient per year outlined in Table 12 was based on the submission's economic model and financial estimates. The PBAC noted that the cost per patient would be lower based on the revised inputs specified in paragraph 7.13.

6.63 The estimated cost per patient was higher in the financial estimates than the economic model (over a 6 year time horizon) because the financial estimates assumed that all patients receive over 6 years of treatment, while the economic model assumed that the proportion of patients who remain on treatment reduces each year (as shown in Table 12).

Estimated PBS usage & financial implications

6.64 This submission was not considered by DUSC. The submission used a mixed epidemiological and market share approach to estimate the use and financial impact of a PBS listing of acalabrutinib in combination with bendamustine and rituximab for

first line treatment of MCL. The key inputs relied on in the financial estimates are summarised in Table 13.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident patients: initiating bendamustine for first line MCL	[redacted][1] patients in Year 1 increasing to [redacted][1] in Year 6 of listing, based on a DUSC analysis (January 2025) of PBS scripts for bendamustine with an Authority code for MCL to June 2024; and a 5% annual growth, based on several arguments: - The changing treatment landscape due to the growing evidence of BTK inhibitors as a treatment alternative to ASCT. - The PBAC previously considered an annual 4.2% growth in total market scripts for R/R MCL was reasonable (Table 16, acalabrutinib PSD, July 2021 PBAC meeting). - Bendamustine historic utilisation data are reflective of the COVID era when the extent of chemotherapy was reduced, therefore the data are likely to be an underestimate. - The increase in efficacy shown in the ECHO trial resulting in more use of bendamustine and rituximab regimens compared to standard chemotherapy.	Estimation of eligible first line MCL patients from bendamustine scripts was reasonable, however the evaluation considered the assumption of 5% annual growth in the market was uncertain. - Transplant-eligible patients would not be permitted to receive treatment with acalabrutinib under the proposed PBS restriction. - The growth rate in the R/R acalabrutinib submission was based on estimates of annual incidence of MCL in Australia from 1982 to 2006 (van Leeuwen 2014), with the study authors suggesting that the increased incidence of MCL may be due to progressive reclassification of SLL as other types of B-cell lymphoma, including MCL. - In the DUSC analysis, the number of incident bendamustine patients increased considerably from 2019/20 to 2020/21 but thereafter appeared to stabilise or slightly decrease.
Uptake rate	Year 1-2: [redacted]%, Years 3-6: [redacted]%. Expected given improved progression free survival with acalabrutinib in the ECHO trial	The evaluation considered that the uptake estimates were assumptions and are uncertain.
Adherence to acalabrutinib treatment	89.0% based on adherence reported in the ECHO trial over the entire treatment period.	Trial-based adherence may not be representative of adherence in clinical practice.
Treatment duration for acalabrutinib	73.73 months, based on mean duration of treatment derived from extrapolated ECHO trial data in the economic model.	The mean duration of treatment was calculated based on a 20 year model time horizon, and assumed all patients receive more than 6 years of treatment. The evaluation and the PBAC considered this was inconsistent with the extrapolated modelled time on treatment curve which estimated that there are 73% of patients on treatment after 1 year, 61% on treatment after 2 years, with a continuing decline in treatment persistence thereafter (in the submission base case economic model). The submission's approach would overestimate the costs of acalabrutinib treatment.
Bendamustine/ rituximab induction	100% of patients, 6 cycles (5.52 months), assumed to apply regardless of the addition of acalabrutinib	The evaluation considered this was reasonable
Duration of rituximab maintenance	With acalabrutinib: 14.78 months; without acalabrutinib 12.89 months. Based on ECHO trial mean duration of rituximab treatment in each treatment arm minus 5.52 months of rituximab induction.	The evaluation considered that this appeared reasonable.

Parameter	Value applied and source	Comment
Proportion of patients initiating subsequent anti-cancer therapy	Submission:19.96% in the initial year of acalabrutinib treatment, decreasing to 3.07% by the patient's 6th year of treatment, derived from the cumulative incidence of subsequent treatment initiation based on extrapolated time to first subsequent therapy used in the economic model. PSCR: 11.9% in the initial year of acalabrutinib treatment, decreasing to 2.9% by the patient's 6th year of treatment	The submission claimed that the time to first subsequent treatment initiation curve was censored for all deaths, however, the economic model used the extrapolated time to first subsequent therapy or death curve, which would overestimate initiation of subsequent first therapy, due to the inclusion of deaths as an event. This was corrected in the PSCR.
Proportion of patients receiving subsequent treatment who will avoid BTK inhibitors in R/R MCL	81% based on the proportion of use of BTK inhibitors as first subsequent therapies in the placebo arm of the ECHO trial (excluding treatments that were neither BTK inhibitors or chemotherapy or that were not available in Australia). Revised to 87.6% in the PSCR.	The submission only included first subsequent treatments received in the trial. In the placebo arm of the trial, of the patients with at least one subsequent MCL therapy, around 87% received a BTK inhibitor. This was corrected in the PSCR.
Duration of subsequent BTK inhibitor treatment	17.8 months, based on the median duration of zanubrutinib treatment in R/R MCL from one of two zanubrutinib single arm studies (Study 206) reported in the July 2021 zanubrutinib consideration (Table 12, zanubrutinib PSD, July 2021 PBAC meeting), as it has the largest market share of all PBS listed BTK inhibitors for R/R MCL.	Results from a later data cut of this study have since been published (Song 2022), with a median follow up of 35.3 months and a median treatment duration of 27.6 months. The PBAC noted the duration of subsequent BTK inhibitors of 17.8 months was consistent with the economic model and considered this was appropriate.

Source: Table 4-1, p148 of the submission.
Abbreviations: BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; PSD, Public Summary Document; PBS, Pharmaceutical Benefits Scheme; R/R, relapsed/refractory
The redacted values correspond to the following ranges:
[1] < 500

6.65 The estimated utilisation and financial implications of a PBS listing of acalabrutinib for previously untreated MCL is summarised in Table 14. The PSCR updated the financial estimates to correct some of the issues with the cost of subsequent BTK inhibitor treatment.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed [a]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Estimated financial implications of acalabrutinib						
Cost to PBS/RPBS less copayments	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Estimated financial implications to other PBS-listed drugs						
Additional rituximab maintenance cost (less copay)	$0	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Cost offsets for reduced subsequent BTKi (less copay)[b]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Cost to PBS/RPBS less copayments (submission)	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Cost to PBS/RPBS less copayments (PSCR)	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]
Net cost to MBS [c]	$0	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost to PBS/RPBS/MBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]
Net cost to PBS/RPBS/MBS (PSCR)	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]

Source: Table 4-4, p152, Table 4-12, p162; Table 4-13, p163; Table 4-14, p164 of the submission; 4.3 Acala UCM March 2025.xlsx
Abbreviations: BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma
[a] Based on 13.04 scripts per patient per year (365.25 days per year/28 days per script) × treatment adherence of 89.02%.
[b] An error in the submission's financial spreadsheet resulted in costs calculated for the first 12 months (of 17.8 months) of BTK inhibitor therapy only. This error was not corrected during the evaluation, but was corrected in the PSCR
[c] Increase in administration costs associated with increased duration of rituximab maintenance therapy with acalabrutinib treatment (6.52 services per year, $123.05 per infusion MBS item number 13950 with 80% rebate)
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *5,000 to < 10,000*
[4] *10,000 to < 20,000*
[5] *$0 to < $10 million*
[6] *$10 million to < $20 million*
[7] *$0 to < $10 million*

6.66 The estimated net cost to the PBS/RPBS of listing acalabrutinib for first line MCL (per the PSCR) was $0 to < $10 million in Year 1 of listing, increasing to $10 million to < $20 million in Year 6, a cumulative total of $30 million to < $40 million over the first 6 years of listing.

6.67 The evaluation and the ESC considered that the estimated financial impact of listing acalabrutinib for first line MCL was uncertain because:

- The average duration of acalabrutinib treatment was derived from the results of the economic model (based on a 20 year time horizon), and assumed all patients receive more than 6 years of treatment. This was inconsistent with the extrapolated

modelled time on treatment curve from the economic model which estimated that there would be decreasing proportions of patients remaining on acalabrutinib treatment over time. The evaluation and the ESC considered the submission's approach would overestimate the costs of acalabrutinib treatment. The PBAC considered that the mean duration of acalabrutinib treatment should be revised to be consistent with the extrapolated modelled time on treatment curve based on the revised economic model outlined by the PBAC (refer to paragraph 7.13) i.e. using the proportion of patients estimated to remain on treatment each year;

- The submission's arguments in support of a 5% annual growth in eligible incident patients were not well supported (see Table 13).
- Acalabrutinib uptake estimates were assumptions and are uncertain.
- The estimated duration of subsequent BTK inhibitor treatment was derived from one of two zanubrutinib single arm studies (Study 206) included in the July 2021 consideration of zanubrutinib for relapsed/refractory MCL. Results from a later data cut of this study have since been published (Song 2022), with a median treatment duration of 27.6 months. The evaluation considered the use of 17.8 months may be underestimated, but noted it was consistent with the median duration of acalabrutinib treatment in relapsed/refractory mantle cell lymphoma in the ACE-LY-004 study reported in the July 2021 acalabrutinib PSD of 17.5 months. The PBAC noted the duration of subsequent BTK inhibitors of 17.8 months was consistent with the economic model and considered this was appropriate.

6.68 Overall, the evaluation and the ESC considered that the submission likely overestimated the cost of listing acalabrutinib.

6.69 The submission stated that a patient access program for acalabrutinib in patients with previously untreated MCL is planned to commence upon TGA registration. The submission estimated approximately < 500 patients will join the patient access program, and these patients would be able to transition to PBS listed acalabrutinib under the proposed restriction. The treatment duration for these grandfathered patients was assumed to exclude the 5.52 month induction period to account for treatment received prior to PBS listing of acalabrutinib. Grandfathered patients were in addition to the estimated incident patients in the first 6 years of listing.

Financial Management – Risk Sharing Arrangements

6.70 The submission noted that there are risk sharing arrangements (RSAs) across all other settings where acalabrutinib is used. RSAs apply for acalabrutinib in first line and relapsed/refractory CLL/SLL and relapsed/refractory MCL. The PBAC has previously considered it appropriate for acalabrutinib and zanubrutinib to join the existing RSA for ibrutinib for relapsed/refractory MCL without revision to expenditure caps (para 6.82, acalabrutinib PSD, July 2021 PBAC meeting; para 6.79, zanubrutinib PSD, July 2021 PBAC meeting).

6.71 However, the submission argued against an RSA for the requested PBS listing for first line acalabrutinib treatment of MCL, stating that financial uncertainty is low, with

discrete and small numbers of eligible patients, and minimal likelihood of use beyond the proposed Authority restriction. Given the submission's claim of increased usage of BTK inhibitors as an alternative to ASCT, the evaluation considered there may be a risk of leakage to patients who are eligible for ASCT. The ESC also considered there may be a risk of use of BTK inhibitors after progression, noting this occurred in 4.3% of patients in the trial. The submission argued that the ECHO trial data is highly applicable to the proposed PBS population and has a long duration of follow-up, therefore PBS usage is expected to closely align with the population modelled in the economic analysis. The submission argued that should the PBAC consider an RSA necessary, the percentage rebate payment beyond the financial caps should be low, given the minimal risk of exceeding the financial estimates.

6.72 Given there is an existing RSA for BTK inhibitors in the relapsed/refractory MCL setting, the evaluation and the ESC considered it may be appropriate for either: a combined RSA across both the first line and relapsed/refractory MCL settings; or for the expenditure caps in the relapsed/refractory setting to be adjusted to account for earlier use.

6.73 In its March 2018 recommendation of ibrutinib for relapsed/refractory MCL, the PBAC advised that an RSA was necessary to achieve cost-effectiveness and that actual utilisation for this indication should be monitored to ensure that cost-effectiveness would be reached (paragraph 12.4, ibrutinib PSD, March 2018 PBAC meeting). The ESC advised that, if a combined RSA across the first- and later-line MCL settings is recommended, then it should be structured to ensure that cost-effectiveness is maintained in the relapsed/refractory setting.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended acalabrutinib (in combination with bendamustine and rituximab (ABR)) for the first line treatment of Stage III or IV mantle cell lymphoma (MCL) in patients who are ineligible for stem cell transplantation. The PBAC noted improvements in progression free survival associated with acalabrutinib for this population. The PBAC considered the submission's economic model included some assumptions that were uncertain and overly optimistic. As such, the PBAC's recommendation was based on, among other matters, its assessment that the cost-effectiveness of acalabrutinib would be acceptable with a price reduction using an economic model respecified by the PBAC. The PBAC further advised that, as the cost-effectiveness of the first line listing relies on reduced use of Bruton tyrosine kinase (BTK) inhibitors in the relapsed/refractory setting, a risk sharing arrangement (RSA) that accounts for reduced use of BTK inhibitors in relapsed/refractory MCL would be required.

7.2 The PBAC was satisfied that ABR provides, for some patients, a significant improvement in efficacy over bendamustine and rituximab.

7.3 The PBAC welcomed the input received via the Consumer Comments facility on the PBS website which outlined the rare and incurable nature of MCL and described the clinical need for more effective treatment options for transplant ineligible patients in the first line setting who have a poor prognosis with existing therapies.

7.4 The PBAC considered that it would be appropriate for the restriction to include separate induction and continuing treatment phases and a grandfather restriction. The PBAC advised that it would be appropriate to add to the initial restriction the clinical criterion, "the condition must be symptomatic". The PBAC further considered it would be appropriate to permit continuation of acalabrutinib if bendamustine and/or rituximab are ceased due to intolerance, and that it is reasonable to restrict BTK inhibitor listings to once in a lifetime.

7.5 The PBAC considered the submission's proposed place in therapy was appropriate, which was as a first line treatment for advanced stage MCL in patients who are ineligible for stem cell transplant, until disease progression. The PBAC noted this was consistent with National Comprehensive Cancer Network (NCCN) guidelines. However, the PBAC noted that there is some evidence emerging for use of BTK inhibitors in transplant eligible patients (in the first line setting) and therefore considered there is a risk of use outside the proposed restriction. The PBAC noted that, over time, use of ABR for the first line treatment of MCL will replace a substantial proportion of use of BTK inhibitors in subsequent lines given these therapies would be limited to once in a lifetime.

7.6 The PBAC considered that the nominated comparator, bendamustine and rituximab, was appropriate.

7.7 The PBAC considered that the submission's claim of superior comparative effectiveness was supported by a well-designed, multi-national, randomised controlled trial (ECHO). The PBAC considered the characteristics of patients enrolled in the ECHO trial were generally representative of the PBS population, but noted the survival data were immature (median 45 months follow up) with the final results expected in 2027.

7.8 The ECHO trial occurred during the COVID-19 pandemic where COVID-19 had a greater impact on deaths, particularly in the ABR arm (i.e. COVID-19 was nominated as a (confirmed or suspected) cause of death for 33 (34%) and 26 (25%) deaths in the acalabrutinib and placebo arms, respectively), as outlined in paragraphs 6.14 and 6.15. The submission presented the results of an analysis in which the OS and PFS results were censored to adjust for COVID-19 related deaths, which the submission claimed was a more accurate representation of the present-day situation. The PBAC considered the hazard ratio for this analysis was associated with a high degree of uncertainty and represented an optimistic sensitivity analysis: as it did not account for competing causes of death; and given the deaths may have reflected the greater impact on immunosuppression when acalabrutinib is added to bendamustine and rituximab.

7.9 The PBAC considered that there was robust evidence to support the primary endpoint of improved progression free survival with ABR compared to bendamustine and rituximab alone, with the ECHO trial reporting a median increase in PFS of 16.8 months, and a HR for PFS of 0.73 (95% CI: 0.57, 0.94) for the full analysis set and 0.64 (95% CI: 0.48, 0.84) for the COVID-19 censored analysis. As such, the PBAC considered that the submission's claim of superior comparative effectiveness was reasonable. However, the PBAC noted a statistically significant benefit was not reported for the secondary endpoints of OS and overall response rate (ORR).

7.10 The PBAC noted the increased risk of infections associated with ABR compared with bendamustine plus rituximab alone, in particular the higher rates of COVID-19 related deaths associated with ABR during the pandemic. Overall, the PBAC considered that the submission's claim of inferior comparative safety was reasonable.

7.11 The PBAC considered that a key limitation of the economic model was that the three health state partitioned survival analysis limited the ability to incorporate the costs and consequences associated with the utilisation of subsequent anti-cancer treatments over the 20-year time horizon (used in the submission base case). The PBAC considered that, given the uncertain OS outcomes and limitations of the model structure, a 10-year time horizon would be more appropriate.

7.12 The submission's economic model included the costs of subsequent BTK inhibitor use in the placebo arm, but not in the ABR arm due to the once in a lifetime rule for BTK inhibitors. However, the PBAC noted that 4.3% of patients in the acalabrutinib arm of the ECHO trial received subsequent BTK inhibitors. The PBAC agreed with the ESC that given that outcomes associated with subsequent BTK inhibitor use could not be removed from the model, it would be appropriate to also include the costs of these therapies in the ABR arm.

7.13 Thus, the PBAC considered that the economic model should be respecified as follows: 10 year time horizon; and BTK inhibitor costs included in the ABR arm consistent with the ECHO trial. The PBAC noted that this resulted in an ICER of $95,000 to < $115,000 per QALY using the full analysis set uncensored for COVID-19, although it reduced to $75,000 to < $95,000 per QALY if the COVID-19 censored analysis were used. The PBAC considered that the most plausible estimate of the ICER would be between these values (given the uncertainty associated with the hazard ratio for the COVID-19 censored analysis, as discussed in paragraph 7.8). The PBAC considered that acalabrutinib would be acceptably cost-effective (using the aforementioned respecified parameters) with an ICER between $55,000 to < $75,000 per QALY (using full analysis set without censoring for COVID-19) and $55,000 to < $75,000 per QALY (using the COVID-19 censored analysis). The PBAC noted a price reduction would be required to achieve these ICERs.

7.14 The PBAC advised the financial estimates should be updated as follows:

- the mean duration of acalabrutinib treatment should be adjusted to be consistent with the extrapolated time on treatment curve from the economic model based on the revised parameters outlined by the PBAC (refer to paragraph 7.13); and

- the price of acalabrutinib should be consistent with paragraph 7.13.

7.15 The PBAC considered that an RSA would be required to help manage the risk of use outside the intended restriction particularly as there is potential for acalabrutinib to be used in patients who are eligible for stem cell transplant, noting that cost-effectiveness has not been evaluated in this setting. Further, the PBAC considered that, given the cost-effectiveness and financial estimates rely on reduced use of BTK inhibitors in the relapsed/refractory setting, a combined RSA across the first line and relapsed/refractory settings would be preferred to ensure these offsets are realised in practice (given BTK inhibitors are subsidised once per lifetime). The PBAC advised that a 100% rebate should apply to any Commonwealth expenditure beyond the agreed estimates (including the revisions to the financial estimates outlined in paragraph 7.14).

7.16 The PBAC noted there is an existing RSA for BTK inhibitors in relapsed/refractory MCL, that is intended to achieve a cost-effective price in this setting, and the PBAC reaffirmed that the intended cost-effectiveness in the relapsed/refractory setting should be maintained going forward.

7.17 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for acalabrutinib:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over bendamustine plus rituximab alone, as while clinically relevant improvements in progression-free survival were evident there was no statistically significant difference in overall survival;

b) The treatment is not expected to address a high and urgent unmet clinical need given the availability of other therapies;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.18 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new listings for acalabrutinib as follows:

Induction:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	New	1	56	5	calquence

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (telephone/electronic (immediate assessment))
Prescribing rule level		**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Episodicity: [blank]
		Severity: Stage III or IV mantle cell lymphoma
		Condition: Mantle cell lymphoma
		Indication: Stage III or IV mantle cell lymphoma
		Treatment Phase: First line therapy - Induction treatment
		Clinical criteria:
		The condition must be previously untreated
		AND
		Clinical criteria:
		The treatment must be initiated in combination with rituximab
		AND
		Clinical criteria:
		The treatment must be initiated in combination with bendamustine
		AND
		Clinical criteria:
		The condition must be symptomatic
		AND
		Clinical criteria:
		Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction
		AND
		Clinical criteria:
		Patients must have a WHO performance status of 2 or less
		AND
		Clinical criteria:
		Patient must not be eligible for stem cell transplantation

Continuing

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB						
acalabrutinib 100 mg tablet, 56		New	1	56	5	calquence
Restriction Summary [new] / Treatment of Concept: [new]						
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (telephone/electronic (immediate assessment))					
Prescribing rule level	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.					
Prescribing rule level	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.					
	Episodicity: [blank]					
	Severity: Stage III or IV mantle cell lymphoma					
	Condition: Mantle cell lymphoma					
	Indication: Stage III or IV mantle cell lymphoma					
	Treatment Phase: First line therapy - Continuing treatment					
	Clinical criteria:					
	Patient must have previously received PBS-subsidised treatment with this drug for this indication					
	AND					
	Clinical criteria:					
	Patient must not have developed disease progression while being treated with this drug for this indication					

Grandfather

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB						
acalabrutinib 100 mg tablet, 56		New	1	56	5	calquence
Restriction Summary [new] / Treatment of Concept: [new]						
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (telephone/electronic (immediate assessment))					
Prescribing rule level	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.					
Prescribing rule level	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.					

	Episodicity: [blank]
	Severity: Stage III or IV mantle cell lymphoma
	Condition: Mantle cell lymphoma
	Indication: ~~Previously untreated~~ Stage III or IV mantle cell lymphoma
	Treatment Phase: First line therapy - Grandfathering treatment – induction and maintenance
	Clinical criteria:
	Patient must have been receiving non-PBS subsidised treatment with this drug for this indication prior to [listing date]
	AND
	Clinical criteria:
	The treatment must have been initiated in combination with rituximab
	AND
	Clinical criteria:
	The treatment must have been initiated in combination with bendamustine
	AND
	Clinical criteria:
	The condition must have been symptomatic prior to being treated with this drug for this indication
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 2 or less prior to being treated with this drug for this indication
	AND
	Clinical criteria:
	Patient must not have been eligible for stem cell transplantation at the time of commencement of this therapy for this indication
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this indication
	AND
	Clinical criteria:
	Patient must not receive more than 6 cycles (12 doses) of PBS and non-PBS subsidised treatment with this drug as induction therapy
	OR
	Patient must have previously received up to a maximum of 6 cycles (12 doses) of this drug as induction therapy

Flow on changes to bendamustine PBS restrictions (for the treatment of MCL, item codes 10760H and 10763L)

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
BENDAMUSTINE HYDROCHLORIDE Injection	10760H (Public) 10763L (Private)	200 mg	11
Available brands			
Bendamustine Juno (bendamustine hydrochloride 100 mg injection, 1 vial)			
Bendamustine Juno (bendamustine hydrochloride 100 mg injection, 1 vial)			
Bendamustine Sandoz			
(bendamustine hydrochloride 25 mg injection, 1 vial)			
Bendamustine Sandoz			
(bendamustine hydrochloride 100 mg injection, 1 vial)			
Restriction Summary [7980] / Treatment of Concept: [7972]			
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required (STREAMLINED)		
Prescribing	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.		
	Episodicity: [blank]		
	Severity: [blank]		
	Condition: [blank]		
	Indication: Previously untreated stage III or IV mantle cell lymphoma		
	Treatment Phase: Induction treatment		
	Clinical criteria:		
	The condition must be CD20 positive		
	AND		
	Clinical criteria:		
	The condition must be previously untreated		
	AND		
	Clinical criteria:		
	The treatment must be in combination with rituximab,		
	OR		
	The treatment must be in combination with rituximab *and acalabrutinib*		
	AND		
	Clinical criteria:		
	The condition must be symptomatic		
	AND		
	Clinical criteria:		
	The treatment must be for induction treatment purposes only		
	AND		
	Clinical criteria:		
	Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction		
	AND		
	Clinical criteria:		
	Patient must not be eligible for stem cell transplantation		

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.