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

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Authority Required listing for acalabrutinib for the treatment of patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) who have received at least one prior therapy and have a WHO performance status of 0 or 1.

1.2 Listing was requested based on a cost-minimisation analysis (CMA) versus ibrutinib.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with MCL that has relapsed or is refractory (R/R) to at least one prior therapy.
Intervention	Acalabrutinib; 100 mg capsule BID until disease progression or unacceptable toxicity.
Comparator	Ibrutinib; 560 mg (4 x 140 mg capsules) once daily until disease progression or unacceptable toxicity.
Outcomes	ORR, PFS, OS and safety.
Clinical claim	In patients with R/R MCL, acalabrutinib is non-inferior compared to ibrutinib in terms of comparative efficacy outcomes of ORR, PFS and OS, and non-inferior in terms of safety, albeit with lower risk of Grade 3-4 thrombocytopenia and atrial fibrillation compared to ibrutinib.

Source: Table 1.1, p17 of the submission.
BID = twice daily; MCL = mantle cell lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression free survival; R/R = relapsed or refractory.

2 Background

Registration status

2.1 Acalabrutinib received provisional TGA registration on 21 November 2019 for a period of 2 years, for the treatment of patients with MCL who have received at least one prior therapy. An application for provisional registration extension was submitted to the TGA on [redacted] and the TGA Delegate has issued an approval letter ([redacted].

2.2 Full registration for acalabrutinib in this indication depends on verification and description of clinical benefit in confirmatory trials, defined as the ACE-LY-004 study ([redacted]) and the ACE-LY-308 trial ([redacted]). The ACE-LY-004 study is a single arm study of acalabrutinib monotherapy for R/R MCL and the ACE-LY-308 trial is a randomised controlled trial comparing bendamustine and rituximab alone versus in combination with acalabrutinib for untreated MCL. The relevance of the ACE-LY-308 trial to the proposed patient population in the current submission is unclear, as the acalabrutinib

combination (not monotherapy) is being studied in previously untreated MCL patients.

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

3 Requested listing

3.1 The requested listing for acalabrutinib is provided below. Secretariat suggestions and additions proposed are shown in *italics* and deletions are in ~~strikethrough~~. The Pre-Sub-Committee Response (PSCR) indicated acceptance of the Secretariat comments/changes to the restriction.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
acalabrutinib 100 mg capsule, 56	12117R	1	56	5	Calquence
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Restriction type: ☒ Authority Required – immediate/real-time assessment by Services Australia					
~~**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.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: *For the purposes of administering this restriction, Bruton tyrosine kinase inhibitors are: acalabrutinib [pending outcome], ibrutinib, zanubrutinib [pending outcome]*					
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.					
Indication: Mantle cell lymphoma					
Treatment Phase: Initial treatment					
Clinical criteria:					
The condition must have relapsed or be refractory to at least one prior therapy					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 0 or 1					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					
~~**AND**~~					
~~**Clinical criteria:**~~					
~~Patient must not have previously received PBS-subsidised treatment with this drug for this condition~~					
AND					
Clinical criteria:					
~~Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of MCL (untreated or relapsed/refractory disease)~~ *Patient must be untreated with Bruton tyrosine kinase inhibitor therapy; or*					
Patient must have developed intolerance to another Bruton~~'s~~ tyrosine kinase ~~(BTK)~~ inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory MCL					
Treatment Phase: Continuing treatment					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					

	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	~~Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition~~
	Patient must not have developed disease progression while being treated with this drug for this condition.
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	Clinical criteria:
	Patient must have received treatment with this drug prior to [insert listing date here]
	Clinical criteria:
	The condition must have relapsed or be refractory to at least one prior therapy prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1 *at the time non-PBS-subsidised treatment with this drug for this condition was initiated.*
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have been untreated with Bruton tyrosine kinase inhibitor therapy at treatment initiation with this drug; or
	Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory MCL
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
	Administrative advice: *Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.*
	Administrative advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*

3.2 The submission proposed a special pricing arrangement that would include a rebate for acalabrutinib such that the cost-minimisation claim is realised once the effective price for ibrutinib is incorporated.

3.3 The proposed restriction is narrower than the TGA indication described in paragraph 2.1, which does not restrict based on WHO performance status or prior treatment with a Bruton tyrosine kinase (BTK) inhibitor.

3.4 The proposed restriction is broadly consistent with the ACE-LY-004 study. While the restriction proposed that patients must have relapsed or be refractory to at least one prior therapy, the study only included patients with 1–5 prior therapies (77% had one or two prior therapies); and while the restriction proposed that patients have a World Health Organisation/Eastern Cooperative Oncology Group (WHO/ECOG) performance status of 0 or 1, the study included patients with an WHO/ECOG status ≤2 (93% had an ECOG status of 0 or 1).

3.5 Under the proposed restriction for acalabrutinib, the ESC noted that patients who have received prior treatment with a BTK inhibitor would not be eligible for treatment with acalabrutinib, except in the case of intolerance to ibrutinib of a severity necessitating permanent treatment withdrawal. Patients who had received prior treatment with BTK inhibitors were excluded from the ACE-LY-004 study. The pre-PBAC response described the proposed restriction as clinically appropriate and consistent with the 2021 NCCN Clinical Practice Guidelines (NCCN, 2021). The pre-PBAC response stated that the proposed listing would extend PBS access to patients who have commenced therapy with ibrutinib or another BTK inhibitor, and have not experienced disease progression, but developed an intolerance necessitating permanent treatment withdrawal (i.e. pre-progression switching). The PBAC considered that the proposed restriction allowing patients who have developed intolerance to another BTK inhibitor necessitating permanent treatment withdrawal to be eligible for treatment with acalabrutinib was appropriate, and that an analogous criterion should flow on to the restriction for ibrutinib in MCL. The PBAC noted that this is consistent with the recommendation for acalabrutinib in R/R chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL) considered at the March 2020 PBAC meeting.

3.6 The submission requested transitioning arrangements ('grandfather' arrangements) for a small number of patients (< 500) who will be treated under an early access program, commencing in March 2021. The pre-PBAC response stated that there were < 500 active R/R MCL patients participating in the access program as of 28 June 2021. The PBAC noted that any transitioning arrangements would serve to capture the same eligibility requirements applying to the usual population.

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

4 Population and disease

4.1 MCL is an aggressive and incurable subtype of B-cell non-Hodgkin's lymphoma. MCL results from malignant transformation of a B lymphocyte in the outer edge of a lymph node follicle (i.e. the mantle zone). The molecular hallmark and initiating oncogenic event in MCL is the t(11;14)(q13;q32) translocation, leading to overexpression of cyclin D1 and causing cell cycle deregulation.

4.2 The median age of diagnosis of MCL is 68 years. Men are three times more likely to be affected (1.3 cases per 100,000 population vs. 0.4 cases per 100,000 population). The National Cancer Institute (2018) estimated 5-year relative survival at 55.9%.

4.3 Due to the aggressive nature of the disease, approximately 60-70% of MCL cases are diagnosed at an advanced stage (Stage III or IV) with disseminated lymphadenopathy, splenomegaly, and bone marrow infiltration. Common symptoms include painless lumps in the neck, groin, or armpit; B symptoms (night sweats, persistent fevers, unexplained weight loss); abdominal bloating; diarrhoea; loss of appetite; and fatigue.

4.4 MCL patients in Australia have multiple rituximab-based immunochemotherapy options available, however these regimens are associated with toxicity issues and are often inappropriate for patients in the relapsed or refractory setting who typically have poor overall fitness. Although patients with newly diagnosed MCL often respond to initial treatment, around 85% do not respond or will relapse within 10 years.

4.5 A BTK inhibitor, ibrutinib, was listed on the PBS for R/R MCL in August 2018. Ibrutinib is associated with high incidences of Grade ≥3 adverse events including infections, anaemia, atrial fibrillation, and thrombocytopenia. In terms of efficacy, 27% of patients achieve a complete response, 43% achieve a partial response, and 30% of patients do not respond to treatment with ibrutinib (Rule 2019).

4.6 This submission has proposed acalabrutinib, also a BTK inhibitor, as an alternative treatment to ibrutinib in the R/R MCL setting. Acalabrutinib has also been proposed for patients who receive ibrutinib as treatment for R/R MCL and develop intolerance requiring permanent treatment withdrawal.

5 Comparator

5.1 The submission nominated ibrutinib as the main comparator. The main reasons were:

- Ibrutinib was PBS listed as treatment for R/R MCL based on superior efficacy and safety compared to immunochemotherapy;
- Ibrutinib is established as the standard of care in R/R MCL;
- Market share for chemotherapy regimens used to treat R/R MCL would be difficult to quantify; and
- Ibrutinib and acalabrutinib are both BTK inhibitors.

5.2 For patients who have not received treatment with ibrutinib and who are not contraindicated, the nominated comparator is appropriate.

5.3 For patients who have received and are intolerant to ibrutinib, or are contraindicated to ibrutinib, immunochemotherapy or supportive care may be a more appropriate comparator.

5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy.

5.5 While the evaluation considered ibrutinib to be an appropriate comparator, the evaluation also identified that immunochemotherapy (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)) could be replaced in clinical practice, which may be less costly than acalabrutinib.

5.6 Zanubrutinib was a near-market comparator and was considered at the July 2021 PBAC meeting in R/R MCL, although not identified as a near-market comparator by the submission.

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 (3) and organisations (3) via the Consumer Comments facility on the PBS website.

6.3 The comments from the healthcare professionals emphasised that acalabrutinib provides a meaningful response in patients, combined with better tolerability compared to the alternative BTK inhibitor, ibrutinib. One healthcare professional indicated they would seek to switch a patient to acalabrutinib under the Sponsor's compassionate access program due to intolerance to ibrutinib. Another healthcare professional commented that the lower rate of atrial fibrillation is clinically meaningful and makes acalabrutinib the preferred BTK inhibitor in patients with a history of this condition.

6.4 The PBAC noted the advice received from Lymphoma Australia, the Leukaemia Foundation, and Rare Cancers Australia, clarifying the likely use of acalabrutinib in clinical practice. The Leukaemia Foundation noted that acalabrutinib is well tolerated by patients, and associated with a lower risk of serious adverse events (AEs) than ibrutinib, particularly neutropenia, Grade 3-4 atrial fibrillation and thrombocytopenia, and that acalabrutinib would be beneficial in patients already at risk of cardiac and haematologic AEs. Lymphoma Australia commented that most MCL patients will relapse after initial remission or may be refractory to first line treatment, and access to acalabrutinib will extend patients' lives whilst allowing them to maintain a good quality of life. The PBAC noted that this advice was supportive of the evidence provided in the submission and similar to the advice provided for zanubrutinib for R/R MCL.

Clinical trials and studies

6.5 No head-to-head trials comparing acalabrutinib to ibrutinib for patients with R/R MCL were identified.

6.6 The submission was based on the following trials and studies:

- One phase II, single-arm, open-label study of acalabrutinib: ACE-LY-004 (N=124).
- One randomised, open-label, phase III study trial comparing ibrutinib versus temsirolimus: MCL-3001/RAY (N= 139 [ibrutinib arm]).
- Three phase II, single-arm, open-label studies of ibrutinib: PCYC-1104 (N=111), MCL-2001/SPARK (N=120), and MCL4001 (N=149).

6.7 The submission presented the following comparisons of acalabrutinib and ibrutinib:

- A naïve comparison (unanchored and without any matching) of acalabrutinib (ACE-LY-004) with four ibrutinib studies (MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK, MCL4001). The ACE-LY-004, MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies were used to compare safety and efficacy. The MCL4001 study was only used to assess comparative safety.
- A naïve comparison of acalabrutinib (ACE-LY-004) and a pooled analysis of three ibrutinib studies (MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK).
- Two unanchored matched adjusted indirect comparisons (MAICs) of acalabrutinib (ACE-LY-004) and a pooled analysis of three ibrutinib studies (MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK).

Table 2 provides details of the trials/studies presented in the submission.

Table 2: Trials, studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Acalabrutinib study		
ACE-LY-004 NCT02213926	An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma. Clinical Study Report.	19 May 2017
	An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma. Clinical Study Report - 24-Month Follow-up Update.	31 July 2018
	Wang M, Rule S, Zinzani P, Goy A, Casasnovas O, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma.	*Leukemia* 2019; 33(11): 2762-6.
	Wang M, Rule S, Zinzani P, Goy A, Casasnovas O, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial.	*The Lancet* 2018; 391(10121): 659-67.
	Wang M, Rule S, Zinzani P, Goy A, Casasnovas O, et al. Efficacy and safety of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma in the phase 2 ACE-LY-004 Study.	59th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2017; 130: S1.
	Wang M, Rule S, Zinzani P, Goy A, Casasnovas O, et al. Long-Term Follow-Up of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma.	*Clinical Lymphoma, Myeloma and Leukemia.* 2019; 19 (Supplement 1): S316.

Trial ID	Protocol title/ Publication title	Publication citation
	Wang M, Rule S, Zinzani P, Goy A, Casasnovas O, et al. Long-term follow-up of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma.	60th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2018; 132.
	Wang M, Rule S, Zinzani P, Goy A, Casasnovas O, et al. Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results from a Phase 2 Study.	Annual Meeting of the American Society of Hematology (ASH). 2020 (abstract 2040 and poster presented at virtual ASH conference).
Ibrutinib trials and studies		
MCL-3001/RAY NCT01646021	Dreyling M, Hermine O, Ribrag V, Sun S, Rizo A, et al. A phase 3 study of ibrutinib versus temsirolimus in patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 1 prior therapy.	*Hematological Oncology* 2013; 31: 274.
	Dreyling M, Jurczak W, Jerkeman M, Silva R, Rusconi C, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: An international, randomised, open-label, phase 3 study.	*The Lancet* 2016; 387(10020): 770-778.
	Freeman C, Jin L, Pararajalingam P, Balasubramanian S, Jiang A, et al. Correlation of the MCL35 score and gene mutations with outcome in patients with relapsed/ refractory (R/R) mantle cell lymphoma (MCL) treated with ibrutinib in the MCL3001 ray trial.	*HemaSphere* 2020; 4 (Supplement 1): 547-8.
	Hess G, Rule S, Jurczak W, Jerkeman M, Santucci R, et al. Lymphoma symptoms: Data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated Mantle Cell Lymphoma (MCL) treated with ibrutinib vs. temsirolimus.	*Blood* 2015; 126 (23): 1542.
	Hess G, Rule S, Jurczak W, Jerkeman M, Santucci Silva R, et al. Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus	*Leukemia and Lymphoma* 2017; 58(12): 2824-2832.
	Lenz G, Balasubramanian S, Goldberg J, Rizo A, Schaffer M, et al. Sequence variants in patients with primary and acquired resistance to ibrutinib in the phase 3 MCL3001 (RAY) trial.	*Haematologica* 2016; 101 (Supplement 1): 155.
	Rule S, Jurczak W, Jerkeman M, Rusconi C, Trneny M, et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study	*Leukemia* 2018; 32(8): 1799-1803.
	Rule S, Jurczak W, Jerkeman M, Santucci R, Rusconi C, et al. Ibrutinib vs temsirolimus: Results from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma (MCL).	*Blood* 2015; 126 (23): 469.
	Rule S, Jurczak W, Jerkeman M, Santucci Silva R, Rusconi C, et al. Ibrutinib vs temsirolimus: Three-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label ray study	*Hematological Oncology* 2017; 35 (Supplement 2): 143-144.

Trial ID	Protocol title/ Publication title	Publication citation
PCYC-1104 NCT01236391	Advani R, Blum K, Truong V, Cheng M, Lee D, et al. Safety and tolerability of bruton's tyrosine kinase (BTK) inhibitor ibrutinib in previously treated mantle cell lymphoma (MCL).	*Journal of Oncology Pharmacy Practice* 2015; 21(2): 20.
	Dreyling M, Wang M, Rule S, Martin P, Goy A, et al. Long-term safety and efficacy of single-agent Ibrutinib in patients with relapsed or refractory mantle cell lymphoma: Updated results of an international, multicenter, open-label phase 2 study.	*Oncology Research and Treatment* 2015; 38: 18-19.
	Jurczak W, Rule S, Martin P, Auer R, Kahl B, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma - Results of an international, multicenter, phase 2 study of Ibrutinib (PCI-32765) - EHA Encore. [Polish].	*Acta Haematologica Polonica.* 2013; 44(3): 314-318.
	Rule S, Wang M, Martin P, Auer R, Kahl B, et al. Updated interim results of an international, multicenter, phase 2 study of ibrutinib (PCI-32765) in relapsed or refractory mantle cell lymphoma.	*Haematologica* 2013; 98: 489.
	Rule S, Wang ML, Martin P, Auer R, Kahl B, et al. Phase 2 study of ibrutinib in relapsed or refractory mantle cell lymphoma: Updated safety analysis on prevalence of infection, diarrhea, and bleeding over time.	*Haematologica* 2014; 99: 150.
	Stilgenbauer S, Rule S, Wang M, Martin P, Auer R, et al. Updated phase 2 safety analysis of prevalence of infection, diarrhea, and bleeding with ibrutinib over time in previously treated mantle cell lymphoma.	*Oncology Research and Treatment* 2014; 37: 34-35.
	Wang M, Rule S, Martin P, Goy A, Auer R, et al. Single-agent ibrutinib demonstrates safety and durability of response at 2 years follow-up in patients with relapsed or refractory mantle cell lymphoma: Updated results of an international, multicenter, open-label phase 2 study.	56th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2014; 124(21).
	Wang M, Rule S, Martin P, Goy A, Auer R, et al. Interim results of an international, multicenter, phase 2 study of BTK inhibitor, ibrutinib (PCI-32765), in relapsed or refractory mantle cell lymphoma (MCL): Durable efficacy and tolerability with longer follow-up.	54th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2012; 120(21).
	Wang M, Rule S, Martin P, Goy A, Auer R, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma.	*New England Journal of Medicine* 2013; 369(6): 507-516.
	Wang M, Rule S, Martin P, Goy A, Auer R, et al. Updated interim results of an international, multicentre, phase 2 study of ibrutinib (PCI-32765) in relapsed or refractory mantle cell lymphoma.	*Hematological Oncology* 2013; 31(1): 194.
	Wang M, Blum K, Martin P, Goy A, Auer R, et al. Long-term follow-up of MCL patients treated with single agent ibrutinib: Updated safety and efficacy results.	*Blood* 2015; 126(6): 739-745.
MCL-2001/ SPARK NCT01599949	Balasubramanian S, Schaffer M, Deraedt W, Davis C, Stepanchick E, et al. Mutational analysis of patients with primary resistance to single-agent ibrutinib in relapsed or refractory Mantle Cell Lymphoma (MCL).	56th Annual Meeting of the American Society of Hematology, (ASH) *Blood* 2014; 124(21).
	Rule S, Goy A, Martin P, Ramchandren R, Alexeeva J, et al. Ibrutinib for the treatment of mantle cell lymphoma (MCL): Evaluating the correlation between patient-reported outcomes and durability of response in a phase 2 study.	*Value in Health* 2015; 18 (3): A300-A1.

Trial ID	Protocol title/ Publication title	Publication citation
	Rule S, Goy A, Martin P, Ramchandren R, Alexeeva J, et al. Single-agent ibrutinib for the treatment of mantle cell lymphoma (MCL): Evaluating the link between durable response and quality of life (QoL) in the SPARK study.	*British Journal of Haematology* 2015; 169: 59.
	Wang M, Goy A, Martin P, Ramchandren R, Alexeeva J, et al. Efficacy and safety of single agent ibrutinib in patients with mantle cell lymphoma who progressed after bortezomib therapy.	56th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2014; 124(21).
MCL4001 NCT01833039	Martin P, Goy A, Ramchandren R, Ferrante L, Reddy V, et al. Safety results from the United States cohort of the ibrutinib early access treatment protocol (EAP: MCL4001) in patients with relapsed or refractory mantle cell lymphoma.	56th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2014; 124(21).
Pooled analysis of ibrutinib studies		
MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK pooled analysis	Rule S, Dreyling M, Goy A, Hess G, Auer R et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies.	*British Journal of Haematology* 2017; 179(3): 430-8.
	Rule S, Dreyling M, Goy A, Hess G, Auer R, Kahl B, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: Extended 3.5-year follow up from a pooled analysis.	*Haematologica* 2019; 104(5): E211-E4.
	Rule S, Dreyling M, Goy A, Hess G, Auer R, Kahl BS, et al. Median 3.5-Year Follow-up of Ibrutinib Treatment in Patients with Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis.	59th Annual Meeting of the American Society of Hematology (ASH) *Blood* 2017; 130(Supplement 1).
	Rule S, Dreyling M, Hess G, Auer R, Kahl B, Cavazos N, et al. Overall survival outcomes in patients with mantle-cell lymphoma (MCL) treated with ibrutinib in a pooled analysis of 370 patients from 3 international open-label studies.	*Haematologica* 2016; 101 (Supplement 1): 155.
	Rule S, Dreyling MH, Goy A, Hess G, Auer R, Kahl BS, et al. Long-term outcomes with ibrutinib versus the prior regimen: A pooled analysis in relapsed/refractory (R/R) mantle cell lymphoma (MCL) with up to 7.5 years of extended follow-up.	61st Annual Meeting of the American Society of Hematology (ASH) *Blood* 2019; 134(Supplement 1).
Matched adjusted indirect comparisons of acalabrutinib and ibrutinib		
ACE-LY-004 and MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK pooled analysis	Matched Adjusted indirect Comparisons of Efficacy and Tolerability Outcomes with Acalabrutinib versus Selected Comparators in Relapsed/Refractory Mantle Cell Lymphoma	No date
	Abstract 2040: Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results From a Phase 2 Study	January 2021
	Telford C, Kabadi S, Abhyankar S, Song J, Signorovitch J, Zhao J, et al. Pcn33 Matching Adjusted Indirect Comparison of Efficacy and Safety of Acalabrutinib Versus Ibrutinib in the Treatment of Relapsed/Refractory Mantle Cell Lymphoma.	*Value in Health* 2019; 22 (Supplement 2): S62.
	Telford C, Kabadi SM, Abhyankar S, Song J, Signorovitch J, Zhao J, et al. Matching adjusted Indirect Comparisons of the Efficacy and Safety of Acalabrutinib Versus Other Targeted Therapies in Relapsed/Refractory Mantle Cell Lymphoma.	*Clinical Therapeutics* 2019; 41(11): 2357-79.e1.

Source: Tables 2.7 & 2.9, pp42-45 & 47 of the submission.

6.8 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population (MCL)	Outcome(s)
Acalabrutinib study (single arm)					
ACE-LY-004	124	Phase II, MC 38.1 mths	Moderate [a]	- One to five previous therapies - ECOG ≤ 2 - Exclude pts with prior BTK treatment	ORR, CR, DoR, PFS, OS, Time to response, HRQoL, AEs
Ibrutinib vs. temsirolimus (only ibrutinib arm used in naïve comparison)					
MCL-3001/RAY	280 (139 IBR)	R, OL, MC 38.7 mths	Unclear	- At least one previous rituximab-containing regimen - ECOG ≤ 1 - Exclude pts with prior BTK treatment	ORR, CR, DoR, PFS, OS, Time to next treatment, Time to response, HRQoL, AEs
Ibrutinib studies (single arm)					
PCYC-1104	111	Phase II, MC 26.7 mths	Moderate [a]	- One to five previous therapies - ECOG ≤ 2	ORR, CR, DoR, PFS, OS, HRQoL, AEs
MCL-2001/ SPARK	120	Phase II, MC 14.9 mths	Moderate [a]	- One to five previous therapies AND at least 1 prior rituximab-containing chemotherapy regimen AND at least 2 cycles of bortezomib therapy - ECOG ≤ 2 - Exclude pts with prior BTK treatment	ORR, CR, PFS, OS, HRQoL, AEs
MCL4001	149	Phase II, MC 4.7 mths [b]	Moderate [a]	- Relapsed or refractory after prior therapy - ECOG ≤ 2 - Exclude pts with prior ibrutinib treatment	AEs
Pooled analysis of ibrutinib studies					
MCL-3001/RAY, PCYC-1004, MCL-2001/ SPARK	370	Pooled analysis 41.4 mths	Moderate [a]	- Per trial populations above	ORR, CR, DoR, PFS, OS, AEs

Source: Tables 2.10, 2.11, 2.13, 2.14, 2.17, 2.22 & 2.24, pp52, 53, 55, 57, 60-62, 71 & 78 of the submission; pp48-52 of the submission; MCL4001 CSR (Attachment 13 of the submission).

[a] Bias assessed using ROBINS-I tool

[b] Bias assessed as unclear in November 2017 PBAC meeting (see paragraph 6.10).

AEs = adverse events; BTK = Bruton's tyrosine kinase; DB = double blind; CR= complete response; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; HRQoL = health related quality of life; IBR = ibrutinib; MC = multi-centre; MCL = mantle cell lymphoma; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression free survival; R = randomised.

6.9 The submission stated that the overall risk of bias for MCL-3001/RAY was assessed as moderate.

6.10 The MCL-3001/RAY trial was included in the November 2016, November 2017, and March 2018 PBAC submissions for ibrutinib as treatment for R/R MCL. At the November 2017 PBAC meeting the risk of bias in MCL-3001 was reported as unclear due to the open-label nature of the trial, and the large differences in patient discontinuations between the trial arms due to AEs and refusing treatment (paragraph 6.10, ibrutinib, Public Summary Document (PSD), November 2017 PBAC Meeting).

6.11 The included studies differed significantly in terms of inclusion/exclusion criteria, baseline disease characteristics and duration of treatment. The evaluation considered that these differences may confound the results of the whole trial comparison.

- The ACE-LY-004, PCYC-1104, and MCL-2001/SPARK studies included patients with a WHO/ECOG performance score ≤ 2 while the MCL-3001/RAY trial included patients with WHO/ECOG performance score ≤ 1; the requested listing specifies a WHO performance status of 0 or 1.
- Patients who received acalabrutinib in the ACE-LY-004 study appear to be healthier than those who received ibrutinib in the MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK studies and the pooled analysis. Patients who received acalabrutinib had less bulky disease, lower risk disease, less Stage IV disease, and fewer patients had lactate dehydrogenase levels above the upper limit of normal compared to patients who received ibrutinib.
- More patients who received acalabrutinib had extra-nodal disease compared with those who received ibrutinib.
- Fewer patients who received acalabrutinib had more than three prior lines of chemotherapy or prior treatment with lenalidomide, bortezomib, stem cell transplant compared with those who received ibrutinib; patients who received acalabrutinib in the ACE-LY-004 study were not required to have had a prior rituximab-containing regimen, whereas ibrutinib patients in the MCL-3001/RAY and MCL-2001/ SPARK trials must have received at least one previous rituximab-containing regimen.
- The median duration of treatment with acalabrutinib in the ACE-LY-004 study was longer than in any of the ibrutinib studies.
- Furthermore, there may be unobserved confounders.

6.12 The ESC considered there is potential for historical bias because the ibrutinib trials were conducted earlier than the acalabrutinib trial, and post-progression treatments were likely different.

6.13 No non-inferiority margins for ORR, PFS and OS were nominated. The submission acknowledged that a lack of a statistically significant difference is not a robust method for determining non-inferiority, but argued that there is no widely accepted minimal clinically important difference (MCID) for ORR, PFS and OS in MCL patients.

Comparative effectiveness

Whole trial analysis

6.14 Table 4 presents the ORR and best response, PFS, and OS reported for each study.

Table 4: Results of ORR, PFS, and OS across the studies

Trial ID	Acalabrutinib	Ibrutinib			
	ACE-LY-004	MCL-3001/ RAY	PCYC-1104	MCL-2001/ SPARK	Pooled [a]
N	124	139	111	120	370
Median follow-up (months)	38.1	38.7	26.7	14.9	41.4
Overall Response Rate					
ORR (CR + PR), n (%) 95% CI (%)	101 (81.5) [b] 74.0, 88.0	107 (77.0) NR	74 (67.0) 57.1, 75.3	75 (62.7) 53.7, 71.8	258 (69.7) 64.1, 75.3 [b]
Best response, n (%)					
CR 95% CI (%) [c]	59 (47.6) 38.8, 56.4	32 (23.0) 16.0, 30.0	26 (23.0) 15.2, 30.8	25 (20.9) 13.6, 28.2	100 (27.0) 22.5, 31.5
PR	42 (33.9)	NR	NR	NR	158 (42.7)
SD	10 (8.1)	NR	NR	NR	43 (11.6)
PD	10 (8.1)	NR	NR	NR	56 (15.1)
Not evaluable	3 (2.4) [d]	NR	NR	NR	NR
Progression free survival					
Patients with progression or death, n (%)	81 (65.3)	NR	NR	NR	NR
Median PFS (months) 95% CI	22.0 16.6, 33.3	15.6 NR	13.0 7.0, 17.5	10.5 4.4, 15.0	12.5 9.8, 16.6
24-month PFS rate, % 95% CI, %	49.6 40.1, 58.4	NR NR	31.0 22.3, 40.4	NR NR	NR NR
Overall survival					
Patients who have died, n (%)	57 (46.0)	77 (55.4)	NR	NR	NR
Median OS (months)	Not reached	30.3	22.5	Not reached	26.7
95% CI	36.5, NE	NR	13.7, NE	NR	22.5, 38.4
24-month OS rate, %	72.4	NR	47.0	NR	NR
95% CI, %	63.5, 79.5	NR	37.1, 56.9	NR	NR

Source: Tables 2.24, 2.25 & 2.27, pp78, 80 & 83 of the submission.

CI = confidence interval; CR = complete response; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease.

[a] Pooled trial data from the MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies for ibrutinib.

[b] Defined as the proportion of pts who achieved PR or better according to the Lugano classification.

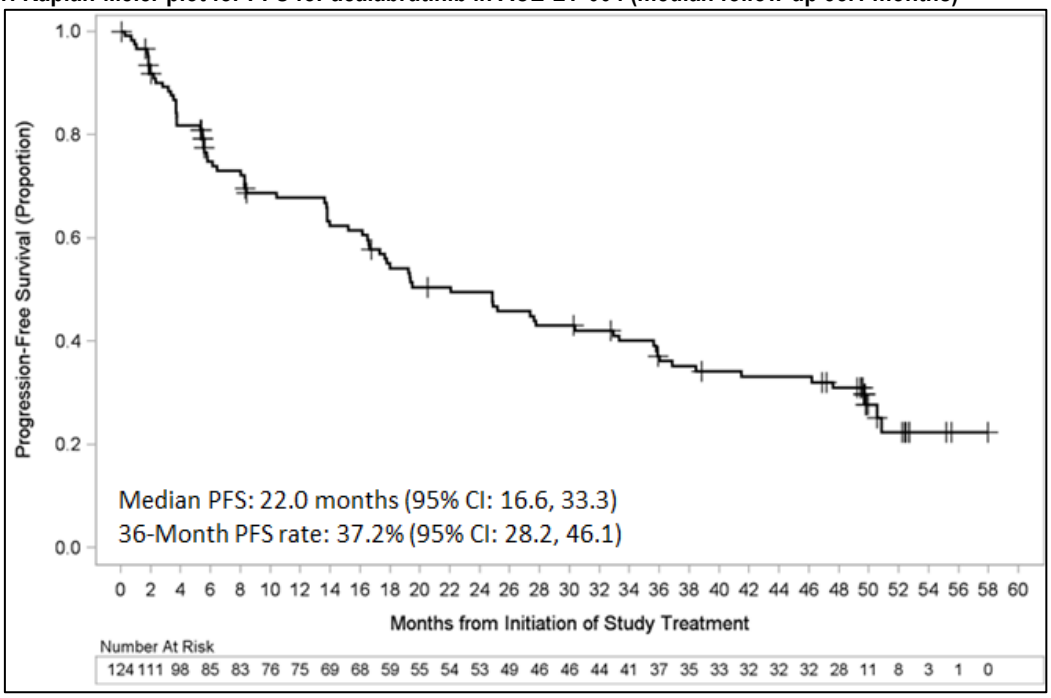
[c] Calculated during the evaluation by first estimating the standard error = SQRT(proportion*[1-proportion]/sample size), then using the NORM.INV function in excel with the observed proportion and estimated standard error to generate upper and lower 95% CIs

[d] Includes pts without any adequate post-baseline disease assessments.

6.15 The ORR observed for acalabrutinib in the ACE-LY-004 study was higher than that observed for ibrutinib in the MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies, individually and pooled (Table 4).

6.16 Figure 1 presents the Kaplan-Meier plot of progression free survival (PFS) from the ACE-LY-004 study at 38.1 months follow-up.

Figure 1: Kaplan-Meier plot for PFS for acalabrutinib in ACE-LY-004 (median follow-up 38.1 months)

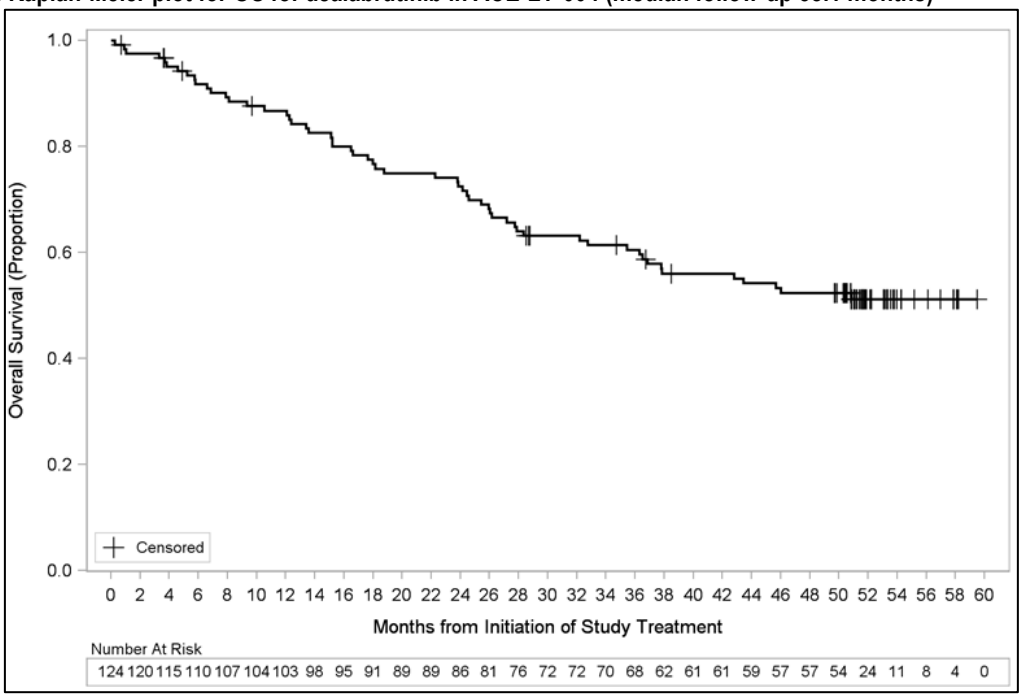


Source: Figure 2.5, p81 of the submission.
CI = confidence interval; PFS = progression free survival.

6.17 Median PFS observed for acalabrutinib in the ACE-LY-004 study was higher than that observed for ibrutinib in the MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies, individually and pooled (Table 4).

6.18 Figure 2 presents the Kaplan-Meier plot of overall survival (OS) from the ACE-LY-004 study at 38.1 months follow-up.

Figure 2: Kaplan-Meier plot for OS for acalabrutinib in ACE-LY-004 (median follow-up 38.1 months)



Source: Figure 2.8, p84 of the submission.
OS = overall survival

6.19 Median OS for acalabrutinib in the ACE-LY-004 study and for ibrutinib in the MCL-2001/SPARK study have not yet been reached (Table 6). OS data for acalabrutinib are immature.

6.20 No data regarding health-related quality of life were presented in the submission. The ACE-LY-004 study collected health-related quality of life data with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ30). The final clinical study report (CSR) (26.3 months median follow-up) reported a small numerical improvement in quality of life at Cycle 2 (month 2) that remained stable until Cycle 27 (month 25). The numerical improvement compared to screening was not considered clinically meaningful.

Matched Adjusted Indirect Comparisons (MAICs)

6.21 The submission presented two unanchored MAICs between acalabrutinib and ibrutinib:

- MAIC 1 matched on baseline characteristics and used ACE-LY-004 data at 15.2 months for ORR and at 26.3 months median follow-up for PFS and OS. Pooled data for ibrutinib at 24-25 months median follow-up was used for ORR, PFS and OS.
- MAIC 2 matched on predictors of PFS and used ACE-LY-004 data at 38.1 months median follow-up and pooled data for ibrutinib at 41.4 months median follow-up for PFS and OS.

6.22 To adjust for differences in baseline characteristics using the MAIC methodology, patients in trials with individual patient data (IPD) are weighted to create weighted mean baseline characteristics that match those reported for trials without IPD (Signorovitch 2012). In this submission, it is possible that IPD from patients in the ACE-LY-004 study were weighted in each MAIC such that the weighted mean baseline characteristics exactly matched those reported for patients in the pooled ibrutinib studies.

6.23 The R programming code and output for MAIC 2 were provided with the submission. The code output matched what was presented in the submission, however it was not possible to verify the MAIC results because:

- IPD were not available,
- The results of MAIC 1 were not provided, and
- The results of MAIC 2 were included in a separate file, rather than in the R log file.

6.24 Baseline characteristics without adjustment and after matching between acalabrutinib and ibrutinib treated patients in MAIC 1 are shown in Table 5. The baseline characteristics considered in MAIC 1 were largely consistent with the key differences in baseline disease characteristics highlighted in paragraph 6.11, however there were also differences in MCL disease stage, prior treatment with lenalidomide or bortezomib, stem cell transplant and treatment duration that were not included in MAIC 1.

Table 5: Baseline characteristics without adjustment and after matching in MAIC 1 (acalabrutinib with 26.3 months median follow-up vs. ibrutinib with 24-25 months median follow-up)

Baseline characteristic	Acalabrutinib (without adjustment) N=123 [a]	ibrutinib N=370	p-value for difference	Acalabrutinib (after matching) ESS=45
	[A], n (%)	[B], n (%)	[A] vs.[B]	[A] %
Age ≥ 65 years	79 (64.2)	231 (62.4)	0.80	62.4
Male	99 (80.5)	289 (78.1)	0.67	78.1
White	91 (74.0)	329 (88.9)	**<0.001**	88.9
WHO/ECOG 0–1	114 (92.7)	346 (93.5)	0.91	93.5
WHO/ECOG=2	8 (6.5)	23 (6.2)	1.00	6.2
WHO/ECOG=3	1 (0.8)	1 (0.3)	0.44	0.3
Low Risk (sMIPI)	48 (39.0)	88 (23.8)	**< 0.01**	23.8
Intermediate Risk (sMIPI)	54 (43.9)	164 (44.3)	1.00	44.3
High Risk (sMIPI)	21 (17.1)	118 (31.9)	**<0.01**	31.9
Tumour Bulk <5 cm	77 (62.6)	189 (51.1)	**<0.05**	51.1
High LDH	33 (26.8)	199 (53.8)	**<0.001**	53.8
Extranodal Disease	89 (72.4)	215 (58.1)	**<0.01**	58.1
Bone Marrow Involvement	62 (50.4)	169 (45.7)	0.42	45.7
Number of Prior Cancer Regimens (1)	59 (48.0)	99 (26.8)	**<0.001**	26.8
Number of Prior Cancer Regimens (2)	37 (30.1)	109 (29.5)	0.99	29.5
Number of Prior Cancer Regimens (≥3)	27 (22.0)	162 (43.8)	**<0.001**	43.8

Source: Table 2.31, p97 of the submission.
ESS = effective sample size; LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; sMIPI = simplified mantle cell lymphoma international prognostic index; WHO = World Health Organisation; **bold =** statistically significant.
a One patient in the ACE-LY-004 trial with missing value in sMIPI prognostic index was excluded from the analysis.

6.25 Baseline characteristics without adjustment and after matching between acalabrutinib and ibrutinib treated patients in MAIC 2 are shown in Table 6. No rationale for matching on predictors of PFS was provided. The submission provided very little information on the selection of PFS predictors.

Table 6: Baseline characteristics without adjustment and after matching in MAIC 2 (acalabrutinib with 38.1 months median follow-up vs. ibrutinib with 41.4 months median follow-up)

	Acalabrutinib (without adjustment) N=122 [a]	ibrutinib N=370	p-value for difference	Acalabrutinib (after matching) ESS=73
	[A] %	[B] %	[A] vs.[B]	[A] %
WHO/ECOG 0–1	93	94	NR	94
Low sMIPI	39	24	NR	24
High LDH	27	55	NR	55
Prior line of therapy ≥2	52	73	NR	73
Bulky disease (≥5cm)	37	49	NR	49
Blastoid histology	11	12	NR	12

Source: Table 2.32, p98 of the submission.
ESS = effective sample size; LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; NR = not reported; sMIPI = simplified mantle cell lymphoma international prognostic index; WHO = World Health Organisation.
[a] Two individuals dropped due to missing values.

6.26 Table 7 presents the ORR and complete response rate without adjustment and after matching in MAIC 1. MAIC 2 did not compare ORR or complete response.

Table 7: ORR without adjustment and after matching in MAIC 1

	Without adjustment				After matching			
	Acalabrutinib N=123 [a]	**Ibrutinib** N=370	**Mean difference (95% CI)**	**p-value**	**Acalabrutinib** ESS=45	**Ibrutinib** N=370	**Mean difference (95% CI)**	**p-value**
	[A] %	[B] %	[A – B]		[A] %	[B] %	[A – B]	
ORR (non-responder imputation), %	74.8	64.6	10.2 (1.1, 19.3)	**<0.05**	73.9	64.6	9.3 (0.3, 18.3)	**<0.05**
CR (non-responder imputation), %	30.1	18.9	11.2 (2.1, 20.2)	**<0.05**	33.8	18.9	14.9 (5.4, 24.3)	**<0.01**

Source: Table 2.33, p99 of the submission, p7, MAIC 26.3 month (Attachment 9 of the submission).
CI = confidence interval; CR = complete response; ESS = effective sample size; MAIC = matching adjusted indirect comparison; ORR = overall response rate; **bold =** statistically significant.
[a] One patient in the ACE-LY-004 trial with missing value in sMIPI prognostic index was excluded from the analysis.

6.27 Without adjustment (i.e., based on a naïve comparison of acalabrutinib and ibrutinib), the mean difference for ORR favoured acalabrutinib (10.2%; 95% confidence interval [CI]: 1.1%, 19.3%; p<0.05). After MAIC 1 adjustment, the mean difference for ORR remained statistically significant (9.3%; 95% CI: 0.3%, 18.3%; p<0.05).

6.28 Without adjustment, the mean difference for complete response favoured acalabrutinib (11.2%; 95% CI: 2.1%, 20.2%; p<0.05). After MAIC 1 adjustment, the mean difference for complete response remained statistically significant (14.9%; 95% CI: 5.4%, 24.3%; p<0.01).

6.29 Table 8 presents PFS and OS without adjustment and after matching in MAIC 1.

Table 8: PFS and OS without adjustment and after matching in MAIC 1

	Without adjustment				After matching			
	Acalabrutinib N=123 [a]	**Ibrutinib** N=370	**Hazard ratio (95% CI)**	**p-value**	**Acalabrutinib** ESS=45	**Ibrutinib** N=370	**Hazard ratio (95% CI)**	**p-value**
Progression free survival								
Median PFS, months (95% CI)	19.5 (16.6,NA)	12.8 (9.3,16.5)	0.67 (0.51,0.88)	**p<0.01**	18.0 (13.7,27.3)	12.8 (9.3,16.5)	0.84 (0.61,1.15)	p=0.27
Overall survival								
Median OS, months (95% CI)	NA (32.2, NA)	25.1 (22.0,NA)	0.55 (0.40,0.78)	**p<0.001**	NA (22.3, NA)	25.1 (22.0,NA)	0.76 (0.47,1.23)	p=0.27

Source: Tables 2.34 & 2.36, pp100 & 102 of the submission.
CI = confidence interval; ESS = effective sample size; MAIC = matching adjusted indirect comparison; NA = not assessable; NA = not assessable; OS = overall survival; PFS = progression free survival; **bold =** statistically significant.
[a] One patient in the ACE-LY-004 trial with missing value in sMIPI prognostic index was excluded from the analysis.

6.30 Without adjustment, the hazard ratio for PFS favoured acalabrutinib (0.67; 95% CI: 0.51, 0.88; p<0.01). After MAIC 1 adjustment, the hazard ratio was no longer statistically significant (0.84, 95% CI: 0.61, 1.15; p=0.27).

6.31 Without adjustment, the hazard ratio for OS favoured acalabrutinib (0.55; 95% CI: 0.40, 0.78; p<0.001). After MAIC 1 adjustment, the hazard ratio was no longer statistically significant (0.76, 95% CI: 0.47, 1.23; p=0.27).

6.32 Table 9 presents PFS and OS without adjustment and after matching in MAIC 2.

Table 9: PFS and OS without adjustment and after matching in MAIC 2

	Without adjustment				After matching			
	Acalabrutinib N=122 [a]	**Ibrutinib** N=370	**Hazard ratio (95% CI)**	**p-value**	**Acalabrutinib** ESS=73	**Ibrutinib** N=370	**Hazard ratio (95% CI)**	**p-value**
Progression free survival								
Median PFS, months (95% CI)	22.0 (NR)	12.8 (NR)	0.75 (0.58,0.96)	**p=0.02**	17.8 (NR)	12.8 (NR)	0.92 (0.74,1.15)	p=0.5
Overall survival								
Median OS, months (95% CI)	Not reached	27.9 (NR)	0.67 (0.49,0.90)	**p=0.007**	36.5 (NR)	27.9 (NR)	0.87 (0.64,1.17)	p=0.35

Source: Tables 2.35 & 2.37, pp101 & 104 of the submission.
CI = confidence interval; ESS = effective sample size; MAIC = matching adjusted indirect comparison; NA = not assessable; NR = not reported; OS = overall survival; PFS = progression free survival; **bold =** statistically significant.
[a] Two individuals dropped due to missing values.

6.33 Without adjustment, the hazard ratio for PFS favoured acalabrutinib (0.75; 95% CI: 0.58, 0.96; p=0.02). After MAIC 2 adjustment, the hazard ratio was no longer statistically significant (0.92, 95% CI: 0.74, 1.15; p=0.5).

6.34 Without adjustment, the hazard ratio for OS favoured acalabrutinib (0.67; 95% CI: 0.49, 0.90; p=0.007). After MAIC 2 adjustment, the hazard ratio was no longer statistically significant (0.87, 95% CI: 0.64, 1.17; p=0.35).

6.35 No non-inferiority margins for PFS and OS were proposed in the submission. The lack of a statistically significant difference in PFS and OS is not sufficient to establish non-inferiority. The upper 95% confidence intervals exceed 1 by only a modest amount, and so may support the non-inferiority claim, despite no non-inferiority margins for PFS and OS being proposed in the submission (paragraph 6.13).

6.36 MAIC 1 assessed ORR and complete response at 15.2 months and PFS, OS and safety at 26.3 months for acalabrutinib versus 24-25 months follow-up for ibrutinib. These data are immature compared with the whole trial analysis at 38.1 months (Table 4).

6.37 Matching of baseline characteristics (MAIC 1) resulted in an effective sample size of 45 (from an original size of 123) and matching of selected predictors of PFS (MAIC 2) resulted in an effective sample size of 73. The ESC agreed with the evaluation that this suggested poor overlap between the study populations. These relatively small effective sample sizes increased the 95% confidence intervals compared to those for the naïve comparisons. Small effective sample sizes indicate that results of the MAIC may be unstable (Phillippo 2018).

6.38 If unanchored forms of population adjustment are to be presented, it is essential that submissions include information on the likely bias attached to the estimates, due to unobserved prognostic factors and effect modifiers distributed differently in the trials (Phillippo 2018). The submission provided no such discussion. For both MAICs, post-matching characteristics for variables not chosen for matching were not provided (paragraphs 6.24 and 6.25). There is an unknown risk of bias due to the potential for missing observed or unobserved effect modifiers or prognostic variables in the MAICs.

Comparative harms

Whole trial analysis

6.39 Table 10 presents the results of safety outcomes in the included studies.

Table 10: Summary of key adverse events in the included studies

	Acalabrutinib		Ibrutinib					
	ACE-LY-004						Pooled	
Trial ID	Short-term follow-up	Long-term follow-up	MCL-3001/ RAY	PCYC-1104	MCL-2001/ SPARK	MCL-4001	Short-term follow-up	Long-term follow-up
N	124	124	139	111	120	149	370	370
Median follow-up, months	26.3	38.1	38.7	26.7	14.9	NR	24-25	41.4
Summary safety outcomes, n (%)								
Any Grade AE	122 (98.4)	NR	NR	111 (100.0)	115 (95.8)	64 (43.0)	364 (98.4)	NR
Any Grade treatment-related AE	93 (75.0)	NR	NR	NR	95 (79.2)	31 (20.8)	NR	NR
Any Grade 3-4 AE	63 (50.8)	NR	104 (74.8)	NR	73 (60.8)	59 (39.6)	265 (71.6)	296 (80.0)
Any SAE	54 (43.5)	NR	79 (56.8)	NR	59 (49.2)	46 (30.9)	NR	232 (62.7)
Discontinuation due to AE	10 (8.1)	14 (11.3)	12 (8.6)	12 (10.8)	20 (16.7)	10 (6.7)	NR	38 (10.3)
Fatal AE	3 (2.4)	6 (4.8)	NR	18 (16.2)	10 (8.3)	20 (13.4)	NR	NR
Grade ≥3, incidence ≥5%, n (%)								
Neutropenia	13 (10.5)	13 (10.5)	18 (12.9)	19 (17.1)	25 (20.8)	10 (6.7)	61 (16.5)	63 (17.0)
Anaemia	13 (10.5)	13 (10.5)	12 (8.6)	12 (10.8)	8 (6.7)	5 (3.4)	30 (8.1)	37 (10.0)
Pneumonia	7 (5.6)	7 (5.6)	NR	9 (8.1)	11 (9.2)	5 (3.4)	33 (8.9)	47 (12.7)
Thrombocytopenia	*5 (4.0)* [a]	NR	13 (9.4)	14 (12.6)	16 (13.3)	5 (3.4)	41 (11.1)	46 (12.4)
Fatigue	2 (1.6)	NR	7 (5.0)	NR	4 (3.3)	NR	16 (4.3)	NR
Diarrhoea	*4 (3.2)* [a]	NR	5 (3.6)	6 (5.4)	3 (2.5)	NR	13 (3.5)	NR
Atrial fibrillation	0 (0.0)	NR	7 (5.0)	7 (6.3)	6 (5.0)	0	17 (4.6)	23 (6.2)
Hypertension	*1(0.8)* [a]	2 (1.6)	NR	NR	NR	NR	19 (5.1)	19 (5.1)

Source: Tables 2.29 & 2.30, pp90 & 92-93 of the submission.

AE = adverse event; n = number of participants reporting data; N = total participants in group; NR = not reported; SAE = serious adverse event.

[a] shown as not reported in the submission – value obtained from ACE-LY-004 CSR 26.3 months (Attachment 6 of the submission)

6.40 Overall, the whole trial analysis of safety suggested the AE profile of acalabrutinib was possibly better than ibrutinib. In particular, the rate of any Grade 3-4 AEs appear lower with acalabrutinib compared to ibrutinib (50.8% vs 71.6% at 26.3 months and 24-25 months follow-up, respectively). However, as with the effectiveness results, the improved safety profile of acalabrutinib may be due to differences in patient baseline disease characteristics.

6.41 Treatment discontinuations due to AEs were similar between acalabrutinib and ibrutinib (11.3% at 38.1 months in the ACE-LY-004 trial vs. 10.3% at 41.4 months in the pooled analysis of the MCL-3001/RAY, PCYC-1104 and MCL-2001/SPARK studies).

6.42 The TGA Product Information for acalabrutinib included special warnings for haemorrhage, infection, cytopenias, secondary primary malignancies, atrial fibrillation and flutter (pp3-4, TGA acalabrutinib Product Information). The submission did not provide whole trial data on haemorrhage or secondary primary malignancies.

6.43 In regard to comparative safety, the ESC noted the recent presentation of results from a head-to-head trial of acalabrutinib and ibrutinib in patients with R/R CLL (ELEVATE-RR trial[1]). The results indicate that acalabrutinib was statistically superior to ibrutinib for atrial fibrillation (9.4% vs. 16.0%; p=0.023) and was also was associated with lower incidence of hypertension, arthralgia, and diarrhoea. However, acalabrutinib was associated with a higher incidence of headache and cough. AEs led to treatment discontinuation in 14.7% of acalabrutinib-treated patients compared with 21.3% of ibrutinib-treated patients. While results from this trial are only available in abstract form without a full statistical analysis, and relate to a different indication, the ESC considered it may provide additional data for assessment of the safety claim. The PBAC agreed with the ESC that the ELEVATE-RR trial provided supportive data of relevance to the current submission.

Matched Adjusted Indirect Comparisons (MAICs)

6.44 The submission did not adequately justify the application of the MAIC methodology to AE data. It is not known if the variables adjusted for in the effectiveness analysis were also relevant variables for the AE analysis. The pre-PBAC response stated that the application of the MAIC methodology to AE data was the same as for efficacy to maintain consistency in the approach and that there is no reason to suggest it would not be applicable to the comparison of safety between acalabrutinib and ibrutinib in this patient population.

[1] First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia by Peter Hillmen. EHA Library; Jun 11 2021; https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324553/peter.hillmen.first.results.of.a.head-to-head.trial.of.acalabrutinib.versus.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dacalabrutinib

6.45 Table 11 summarises the key safety results for the ACE-LY-004 study and pooled analysis for the MCL-3001/RAY, PCYC-1104 and MCL-2001/SPARK studies without adjustment and after matching on baseline characteristics (MAIC 1; Table 5).

Table 11: Key adverse events without adjustment and after matching in MAIC 1 (26.3 months follow-up)

	Without adjustment				After matching			
	ACA N=123	**IBR** N=370	**Mean difference (95% CI)**	**p-value**	**ACA** ESS=45	**IBR** N=370	**Mean difference (95% CI)**	**p-value**
	[A] %	[B] %	[A – B]		[A] %	[B] %	[A – B]	
Summary safety outcomes, n (%)								
Any Grade 3-4 AE	52.8	71.6	-18.8 (-28.7,-8.8)	**<0.001**	66.5	71.6	-5.1 (-15.0,4.8)	0.31
Grade ≥3, incidence ≥5%, n (%)								
Neutropenia	10.6	16.5	-5.9 (-1.26, 0.7)	0.08	18.4	16.5	1.9 (-9.7,13.6)	0.74
Anaemia	10.6	8.1	2.5 (-3.7, 8.6)	0.43	14.7	8.1	6.6 (-3.7, 8.6)	0.43
Thrombocytopenia	4.1	11.1	-7.0 (-11.8,-2.3)	**<0.01**	4.0	11.1	-7.1 (-12.4,-1.7)	**<0.01**
Diarrhoea	3.3	3.5	-0.2 (-3.9, 3.4)	0.89	1.7	3.5	-1.8 (-4.5, 0.9)	0.19
Atrial fibrillation	0	4.6	-4.6 (-6.7, -2.5)	**<0.001**	0	4.6	-4.6 (-6.7, -2.5)	**<0.001**
Major bleeding	2.4	4.9	-2.5 (-6.0, 1.1)	0.17	2.3	4.9	-2.6 (-6.8, 1.6)	0.22

Source: Table 2.38, pp104-105 of the submission.
ACA = acalabrutinib; AE = adverse event; CI = confidence interval; ESS = effective sample size; IBR = ibrutinib; MAIC = matching adjusted indirect comparison; n = number of participants reporting data; N = total participants in group; **bold =** statistically significant.

6.46 Without adjustment, the rate of Grade ≥3 AEs was lower for acalabrutinib (52.8% vs. 71.6%; mean difference = -18.8%; 95% CI: -28.7%, -8.8%; p<0.001). The rate of Grade ≥ 3 thrombocytopenia was lower for acalabrutinib (4.1% vs. 11.1%; mean difference = -7.0%; 95% CI: -11.8%, 2.3%; p<0.01). The rate of Grade ≥3 atrial fibrillation was also lower for acalabrutinib (0.0% vs. 4.6%; mean difference = -4.6%; 95% CI: -6.7%, 2.5%; p<0.001). This was based on an earlier follow-up (26.3 months for acalabrutinib and 24-25 months for ibrutinib). The whole trial results at this time point and with longer follow-up are presented in presented in Table 10.

6.47 After MAIC 1 adjustment, the mean difference for Grade ≥3 AEs was no longer statistically significant (-5.1%; p=0.31). The mean difference of Grade ≥3 thrombocytopenia (-7.1%; p<0.01) and Grade ≥3 atrial fibrillation (-4.6%; p<0.001) remained statistically significantly lower for acalabrutinib than ibrutinib. The results should be interpreted with caution due to inadequate justification of use of the MAIC 1 methodology for AEs, and the small effective sample size in the acalabrutinib arm.

6.48 There were substantial gaps in the safety results presented for MAIC 1 compared with the whole trial analysis. The only summary safety outcome provided was 'Any Grade 3-4 AE'. Discontinuations due to AE were not presented. Pneumonia, fatigue, and hypertension Grade ≥3 were not presented.

6.49 Haemorrhage/major bleeding was not presented as an outcome in the whole trial analysis but was included in MAIC 1. There were fewer major bleeding events Grade ≥3 with acalabrutinib than ibrutinib without adjustment and after matching, however the difference was not statistically significant in either setting.

6.50 Table 12 summarises the key safety results of the ACE-LY-004 study and pooled analysis for the MCL-3001/RAY, PCYC-1104 and MCL-2001/SPARK studies without adjustment and after matching on predictors of PFS (MAIC 2; Table 6).

Table 12: Key adverse events without adjustment and after matching in MAIC 2 (38.1 months median follow-up)

	Without adjustment				After matching			
	ACA N=122	**IBR** N=370	**Risk difference (95% CI)**	**p-value**	**ACA** ESS=73	**IBR** N=370	**Risk difference (95% CI)**	**p-value**
	[A] %	[B] %	[A – B]		[A] %	[B] %	[A – B]	
Grade ≥3, incidence ≥5%, n (%)								
Neutropenia	11.4	17.0	NR	NR	15.0	17.0	-2.0 (-11.4,7.4)	p=0.7
Anaemia	10.6	10.0	NR	NR	14.8	10.0	4.8 (-4.3, 14)	p=0.3
Pneumonia	6.5	12.7	NR	NR	8.7	12.7	-4.0 (-11.7,3.7)	p=0.3
Thrombocytopenia	4.1	12.4	NR	NR	5.3	12.4	-7.1 (-13.3,-0.8)	**p<0.05**
Atrial fibrillation	0.0	6.2	NR	NR	0	6.2	-6.2 (-8.7, -3.7)	**p<0.001**
Hypertension	1.6	5.1	NR	NR	2.6	5.1	-2.5 (-7.4, 2.0)	p=0.3

Source: Table 2.39, p105 of the submission.
ACA = acalabrutinib; AE = adverse event; CI = confidence interval; ESS = effective sample size; IBR = ibrutinib; MAIC = matching adjusted indirect comparison; n = number of participants reporting data; N = total participants in group; **bold =** statistically significant.

6.51 After MAIC 2 adjustment, the risk difference of Grade ≥3 thrombocytopenia (-7.1; p<0.05) and Grade ≥3 atrial fibrillation (-6.2; p<0.001) were statistically significantly lower for acalabrutinib than ibrutinib. The results should be interpreted with caution due to inadequate justification of use of the MAIC 2 methodology for adverse events, and the small effective sample size in the acalabrutinib arm.

6.52 There were substantial gaps in the safety results presented for MAIC 2 compared with the data provided in the whole trial analysis. No summary safety outcomes were presented. No information on haemorrhage/major bleeding was presented.

6.53 While treatment discontinuations due to AEs were similar between acalabrutinib and ibrutinib for the whole trial analysis (paragraph 6.41), the ESC noted that treatment discontinuations due to AEs for the MAIC analyses were not presented. The ESC considered that the statistical difference observed for individual AEs in the MAICs (thrombocytopenia and atrial fibrillation) should also be considered in the context of the overall treatment discontinuation due to AEs.

Benefits/harms

6.54 A summary of the comparative harms for acalabrutinib versus ibrutinib based on MAIC 2 (after matching) is presented in Table 13.

Table 13: Summary of comparative harms for acalabrutinib and ibrutinib

Harms						
	Acalabrutinib n/N	Ibrutinib n/N	RR (95% CI)	Event rate/100 patients [a]		RD (95% CI)
				Acalabrutinib	Ibrutinib	
Thrombocytopenia						
MAIC 2 (ACE-LY-004 vs pooled [b])	NR	NR	NR	5.3	12.4	-7.1 (-13.3,-0.8)
Atrial fibrillation						
MAIC 2 (ACE-LY-004 vs pooled [b])	NR	NR	NR	0	6.2	-6.2 (-8.7, -3.7)

Source: Table 2.39, p105 of the submission.
HR = hazard ratio; PBO = placebo; RD = risk difference; MAIC = matching adjusted indirect comparison.
[a] Median duration of follow-up: ACE-LY-004 = 38.1 months; pooled analysis of ibrutinib studies [b] = 41.4 months; expected median duration of treatment = 14.4 months.
[b] Pooled data from the MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies for ibrutinib.

6.55 On the basis of MAIC 2 comparing acalabrutinib and ibrutinib in the submission, patients treated with acalabrutinib would experience a similar duration of PFS and OS compared to ibrutinib, and for every 100 patients treated with acalabrutinib in comparison with ibrutinib:

- Approximately 7 fewer patients would experience Grade ≥3 thrombocytopenia.
- Approximately 6 fewer patients would experience Grade ≥3 atrial fibrillation.

Clinical claim

6.56 The submission described acalabrutinib as at least non-inferior in terms of efficacy (ORR, PFS and OS) compared to ibrutinib. After MAIC 1 adjustment, the mean difference for ORR and CR remained statistically significant and favoured acalabrutinib. While PFS and OS lost statistical significance after matching in MAIC 1 and 2, the data may support non-inferiority. However, there were several key issues that create uncertainty regarding the efficacy claim, as follows:

- The clinical evidence consisted of a single arm, open label study (ACE-LY-004, N=124) that compared acalabrutinib to ibrutinib by naïve comparisons and two unanchored MAICs. The pre-PBAC response reiterated that the clinical comparison of acalabrutinib to ibrutinib in R/R MCL was based on the best available evidence, comprising a naïve indirect comparison supplemented with two unanchored MAICs to adjust for observed cross-trial differences in baseline characteristics.
- The included studies differed significantly in terms of inclusion/exclusion criteria (WHO/ECOG performance status and prior rituximab treatment) and baseline disease characteristics (acalabrutinib patients appeared healthier with less bulky

disease). These differences may confound the results of the whole trial comparison.

- No non-inferiority margins for ORR, PFS and OS were nominated. According to Section 2.4.5 of the PBAC Guidelines (v5.0), the lack of a statistically significant difference may not be sufficient to establish non-inferiority. The PSCR stated that a non-inferiority margin was not nominated for the acalabrutinib R/R CLL/SLL submission considered at the March 2020 PBAC meeting, yet the PBAC accepted that the evidence, while uncertain, supported a claim of non-inferior comparative effectiveness compared to ibrutinib.
- After matching, the upper confidence intervals for PFS and OS in the unanchored MAICs were slightly greater than one, which suggested non-inferiority is reasonable. However, the evaluation considered the results were uncertain for the following reasons:
    - Unanchored MAICs make strong assumptions that are very hard to meet. For example, ''conditional constancy of absolute effects'' means that the absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables, and all effect modifiers and prognostic variables are required to be known. While the PSCR stated that "it is reasonable to assume all important variables that could be considered effect modifiers and prognostic factors have been taken to account and adjusted for," there was no discussion of potential bias or presentation of post-matching characteristics for variables not chosen for matching. The pre-PBAC response stated that the efficacy results are consistent between MAIC1 and MAIC2, in that they showed a statistically significant clinical benefit for acalabrutinib compared with ibrutinib before matching and a numerical trend favouring acalabrutinib after matching.
    - MAIC 1 and MAIC 2 resulted in an effective sample size of 45 and 73, respectively. The ESC agreed with the evaluation that this suggested poor overlap between the trial populations. Small effective sample sizes indicate that the results of the MAIC may be unstable.
    - MAIC 1 assessed ORR at 15.2 months and PFS, OS and safety at 26.3 months for acalabrutinib versus 24-25 months follow-up for ibrutinib. The PFS and OS data are immature.
    - In MAIC 2, very little information was provided on the selection of PFS predictors. There is a higher risk of bias compared to MAIC 1 due to a larger number of potential confounders.
    - For both MAICs, post-matching characteristics for variables not chosen for matching were not provided. There is an unknown risk of bias due to the potential for missing observed or unobserved effect modifiers or prognostic variables in the MAICs.

6.57 The submission described acalabrutinib as non-inferior in terms of safety compared to ibrutinib, albeit with lower risk of Grade 3-4 thrombocytopenia and atrial fibrillation. The key issues were:

- As with the efficacy evidence, there were no head-to-head trials comparing acalabrutinib and the results of the unanchored MAICs were considered uncertain.
- The TGA PI for acalabrutinib included special warnings for haemorrhage/major bleeding and secondary primary malignancies. The submission did not present whole trial data for either of these events.
- There were substantial gaps in the safety results presented for both MAICs. MAIC 1 only presented summary data for 'Any Grade 3-4 AE' and did not present data for Grade ≥3 pneumonia, fatigue, or hypertension (paragraph 6.48). MAIC 2 did not present any summary safety data or results for Grade ≥3 haemorrhage/major bleeding (paragraph 6.52).
- The ESC noted that the submission did not adequately justify the application of the MAIC methodology to AE data. It is not known if the variables adjusted for in the effectiveness analysis were also relevant variables for the AE analysis.

6.58 The PBAC agreed with the ESC that while uncertain, the claim of non-inferior comparative effectiveness was reasonable, noting that the efficacy results were broadly consistent across analyses, and showed a statistically significant clinical benefit for acalabrutinib compared with ibrutinib before matching and a numerical trend favouring acalabrutinib after matching.

6.59 The PBAC agreed with the ESC that the claim of non-inferior comparative safety was reasonable. The PBAC acknowledged the data in indications other than MCL (namely R/R CLL) suggested that treatment with acalabrutinib may be associated with a lower rate of AEs compared with ibrutinib, including lower rates of atrial fibrillation, however based on the limited single arm data currently available for acalabrutinib in MCL, the PBAC considered that a conclusion of non-inferior safety was appropriate.

Economic analysis

6.60 The submission presented a CMA of acalabrutinib versus ibrutinib based on the claim of non-inferior efficacy and non-inferior safety, albeit with lower risk of Grade 3-4 thrombocytopenia and atrial fibrillation. A cost-minimisation approach is consistent with the clinical claim.

6.61 The equi-effective doses were estimated as:

- Acalabrutinib 100 mg twice daily, taken orally until disease progression or unacceptable toxicity, and
- Ibrutinib 560 mg once daily, taken orally until disease progression or unacceptable toxicity.

6.62 The proposed equi-effective doses were consistent with the medicine doses and treatment regimens in the ACE-LY-004 MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies and the TGA Product Information for acalabrutinib and ibrutinib.

6.63 In addition to the equi-effective doses calculated above, the following parameters were included in the CMA:

- The median time on treatment for acalabrutinib and ibrutinib (14.4 months) was from the MCL-3001/RAY trial at 38.7 months follow-up (unadjusted).
- The relative dose intensity for acalabrutinib (98.6%) was from the ACE-LY-004 study at 38.1 months follow-up (unadjusted). The relative dose intensity for ibrutinib (99.9%) was from the MCL-3001/RAY trial at 20 months follow-up (unadjusted). Applying these relative dose intensities to the CMA results in a higher price for acalabrutinib.
- AE rates were estimated from MAIC 2 (38.1 months follow-up for acalabrutinib and 41.4 months follow-up for ibrutinib) (post-MAIC adjustment) and hospitalisation costs associated with Grade ≥3 thrombocytopenia and atrial fibrillation based on Australian refined diagnosis-related groups and the 2021-22 National Efficient Price.

6.64 At the latest data cut in each study, the median duration of treatment was longer for acalabrutinib (17.5 months, at 38.1 months median follow up in the ACE-LY-004 trial) than for ibrutinib (14.4 months, at 38.7 months median follow up in the MCL-3001/RAY study). This does not support the assumption of equal duration of treatment (14.4 months) with acalabrutinib and ibrutinib. However, the observed differences in duration of treatment could be due to differences in trial inclusion/exclusion criteria and patients' baseline disease characteristics (paragraph 6.11). Mean duration of treatment for the MCL-3001/RAY trial is unpublished and median duration of treatment in the ACE-LY-003 study underestimated mean duration of treatment (paragraph 6.80).

6.65 In its consideration of acalabrutinib as treatment for patients with R/R CLL/SLL, the PBAC considered that the CMA should not include AE costs due to the unreliability of the data presented in the MAIC (paragraph 7.11, acalabrutinib, PSD, March 2020 PBAC meeting). While the PSCR stated that "cost offsets associated with reduced risk of these [adverse] events were claimed in the cost minimisation as they are expected to translate to cost savings in clinical practice," the ESC considered that this claim was uncertain due to its reliance on the results of an unanchored MAIC with a small effective sample size and matching based on predictors of PFS.

6.66 The results of the CMA based on the published AEMP of ibrutinib are presented in Table 14.

Table 14: Results of the cost-minimisation analysis

Component	Acalabrutinib	Ibrutinib
Medicine costs		
Cost per pack (AEMP/PEMP) [a]	$[redacted]	$11,511
Days per pack	28	30
Cost per day	$[redacted]	$384
Treatment duration (months)	14.4	14.4
Relative dose intensity	98.60%	99.9%
Packs per treatment course [b]	15.43	14.59
Cost per treatment course	$[redacted] [c]	$167,924 [c]
Additional costs		
Thrombocytopenia (Grade 3-4)	$93	$205
Atrial fibrillation (Grade 3-4)	$0	$83
Total cost per treatment course	$[redacted]	$168,212

Source: Tables 3.5 & 3.6, p118 of the submission, p118 of the submission, Acalabrutinib_Costminmodel (Attachment 22 of the submission).
Italicised values.
AEMP = approved ex-manufacturer price; PEMP = proportional ex-manufacturer price.
[a] published AEMP/PEMP.
[b] added during the evaluation.
[c] value cannot be replicated using data in the submission tables due to rounding but is consistent with the CMA model.

6.67 The ESC noted that for patients who have developed an intolerance to ibrutinib necessitating permanent treatment withdrawal, and then go on to receive acalabrutinib as per the requested listing (paragraph 3.5), the duration of therapy for acalabrutinib after initial exposure to ibrutinib is unknown and has not been accounted for in the CMA.

6.68 The PBAC considered that the cost-minimisation approach must establish that the cost per patient for treatment with acalabrutinib would be no more than the cost per patient of ibrutinib. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy, and also accounts for any difference in the mean duration of treatment, relative dose intensity, and cost offsets associated with reductions in AEs. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

6.69 The ESC noted that the CMA draws from a limited clinical evidence base that used naïve comparisons and 2 unanchored MAICs. To limit the consequences of the clinical uncertainty, the ESC recommended adjustment of the parameters included in the CMA as follows.

- The median time on treatment for each agent should reflect the clinical trial data: 17.5 months for acalabrutinib at 38.1 months median follow-up, and 14.4 months for ibrutinib at 38.7 months median follow-up. The ESC considered that the assumed equal duration of treatment for acalabrutinib and ibrutinib (14.4 months) was not justified given the median length of treatment in the pivotal acalabrutinib study for which non-inferiority has been established was longer (17.5 months).

- The cost offsets for a reduction in AEs (Grade ≥3 thrombocytopenia and atrial fibrillation) should be removed, as the submission did not adequately justify the application of the MAIC methodology to AE data (paragraph 6.44), and the ESC considered that incorporation of cost offsets for reduction in AEs was not consistent with the clinical claim of non-inferior safety.
- The relative dose intensities (RDIs) of acalabrutinib and ibrutinib should be equivalent.

6.70 The pre-PBAC response stated that in the absence of head-to-head comparisons for treatment duration, the CMA was conducted assuming a consistent median treatment duration of 14.4 months (as a proxy) for both acalabrutinib and ibrutinib and noted this approach is similar to that accepted in the CMA for R/R CLL, where the PBAC accepted acalabrutinib and ibrutinib would have equivalent treatment duration (paragraph 7.1, acalabrutinib PSD, March 2020). The pre-PBAC response maintained this assumption is reasonable given median time on treatment for acalabrutinib in ACE-LY-004 (13.8 months at 15.2 months median follow-up in the CSR), and ibrutinib in RAY (14.4 months at 20.0 months median follow-up) were comparable at similar follow-up times.

6.71 The PBAC considered that a revised base case was necessary, with adjustments to assumptions for median treatment duration, AEs and RDIs as proposed by the ESC. The PBAC agreed with the ESC that the CMA should assume the median treatment durations from the latest data cut in each study, noting that despite the median follow-up being similar for both studies, the median duration of treatment was longer for acalabrutinib (17.5 months, at 38.1 months median follow up in the ACE-LY-004 trial) compared with ibrutinib (14.4 months, at 38.7 months median follow up in the MCL-3001/RAY study). The PBAC agreed with the ESC that to ensure the cost per patient treated with acalabrutinib is no more than for ibrutinib, that the cost offsets for AEs and adjustments for RDIs should not be included in the CMA given the clinical uncertainty associated with the inputs informing these costs.

Drug cost/patient/course

6.72 Table 15 presents the drug cost per patient per course. The proposed published AEMP for acalabrutinib was $[redacted] (DPMQ = $[redacted]).

6.73 The submission assumed a median duration of treatment of 14.4 months for acalabrutinib and ibrutinib since mean duration of treatment has not been published for the MCL-3001/RAY trial. Applying the mean duration of treatment from the ACE-LY-004 study (23.5 months) increases the cost of acalabrutinib.

Table 15: Drug cost per patient for proposed and comparator drugs (published DPMQ)

	Acalabrutinib Trial dose and duration	Acalabrutinib Model	Acalabrutinib Financial estimates	Ibrutinib Trial dose and duration	Ibrutinib Model	Ibrutinib Financial estimates
Mean dose	192.3 mg/day [a]	-	-	-	-	-
Median dose	-	197.2 mg/day [b]	197.2 mg/day [b]	559.2 mg/day [b]	559.2 mg/day [b]	559.2 mg/day [b]
Mean duration	23.5 months	-	-	-	-	-
Median duration	-	14.4 months	14.4 months	14.4 months	14.4 months	14.4 months
Cost/patient/month	$[redacted] [c]	$[redacted] [c]	$[redacted] [c]	$13,780 [c]	$11,825 [c]	$11,825 [c]
Cost/patient/course	$[redacted] [d]	$[redacted] [e]	$[redacted] [e]	$198,428 [f]	$170,275 [g]	$170,275 [g]

Source: Table 4.5, p125 of the submission; ACE-LY-004 38.1 months Table 11.3.1.1 (Attachment 21 of the submission); Acalabrutinib_Costminmodel (Attachment 22 of the submission).
DPMQ = Dispensed Price for Maximum Quantity.
[a] ratio of actual cumulative dose and duration of exposure
[b] prescribed dose * median dose intensity
[c] (cost/patient/course) / mean duration (months)
[d] ([dose/day * mean duration (days)]/ 100mg / 56 capsules), rounded up * cost-minimised DPMQ.
[e] (results sheet, cell D25) * (drug costs sheet, cell D16) of Acalabrutinib_Costminmodel
[f] ([dose/day * mean duration (days)]/ 120mg / 120 capsules), rounded up * DPMQ.
[g] (results sheet, cell E25) * (drug costs sheet, cell D17) of Acalabrutinib_Costminmodel

Estimated PBS usage & financial implications

6.74 DUSC considered the submission.

6.75 The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of acalabrutinib. Table 16 presents the key inputs used in the financial estimates.

Table 16: Key inputs for financial estimates

Data	Value	Source	Comment
Treatment utilization			
Utilisation of ibrutinib for R/R MCL – Year 2020	2,514	Medicare Statistics PBS Item reports for 11419B.	This is appropriate.
Rate of yearly growth in R/R MCL total market scripts	4.2% per year	Assumed to follow growth rate of yearly MCL incidence as reported in van Leeuwen (2014).	This evaluation considered this assumption to be reasonable and noted that alternative assumptions were tested in the submission. However, the DUSC considered that steady state has not yet been reached in the MCL market as there was a 26.1% increase in the number of ibrutinib scripts dispensed between 2019 and 2020 (see paragraph 6.81).
Rate of R/R MCL market growth due to acalabrutinib listing	Nil	Assumption.	This assumption is inconsistent with the restriction and the population defined in the submission. There may be untreated patients at higher risk of bleeding and cardiac AEs who may receive treatment with acalabrutinib. Further, the submission assumed that non-progression treatment switching would be captured in the market share estimates. The cost-minimisation analysis and financial estimates were modelled using a median treatment duration of 14.4 months, which included patients who discontinue early due to adverse events. Patients who discontinue ibrutinib early and commence treatment with acalabrutinib would be in addition to those

Data	Value	Source	Comment
			who commence ibrutinib/acalabrutinib as their first BTK inhibitor, which could increase the market size. The DUSC agreed with the evaluation that the submission's claim that the listing of acalabrutinib will not grow the market is not consistent with the claim made in Section 1. DUSC considered there may be a proportion of patients who are eligible for ibrutinib treatment but are not receiving treatment due to contraindications, and these patients were not included in the financial estimates. Contraindications to ibrutinib may include patients with arrhythmias, at higher risk of bleeding or those on anticoagulants. Furthermore, patients who are hesitant to be treated with ibrutinib and patients who ceased ibrutinib due to intolerance may switch to acalabrutinib.
Script ratio of acalabrutinib versus ibrutinib	1.06 [a]	Assumed median duration of treatment (14.4 months), adjusted for differences in duration of treatment per pack (28 for ACA, 30 for IBR) and RDI (98.6% for ACA, 99.9% for IBR).	The calculation method is reasonable, and the inputs are consistent with the cost-minimisation analysis. Applying trial-based treatment durations changes the script ratio. The DUSC considered that the assumed equal duration of treatment for acalabrutinib and ibrutinib was not appropriate and would underestimate utilisation given the median length of treatment in the pivotal acalabrutinib study, for which non-inferiority has been established, was longer (17.5 months).
Market share			
Uptake rate (market share of acalabrutinib after listing)	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Assumption.	This assumption was not justified. Furthermore, it is not consistent with the clinical claim of "non-inferior in terms of safety albeit with lower risk of Grade 3-4 thrombocytopenia and atrial fibrillation" (submission). The market share may be underestimated. Alternative assumptions were tested in the submission.
Costs			
Acalabrutinib DPMQ	$[redacted]	Requested price.	This is consistent with the cost-minimised price presented in the submission.
Ibrutinib DPMQ	$11,672.21	PBS item number 11419B.	Submission presents values rounded to nearest dollar. Prices in the model match the PBS.
MBS costs	Nil	Assumption	This is reasonable.

Source: Tables 4.1 to 4.7, pp121, 123-126 of the submission; pp126-127 of the submission, sheet 'Background and Assumptions' of Acalabrutinib BIM.

ACA = acalabrutinib; AEs = adverse events; BIM = budget impact model; BTK = Bruton's Tyrosine Kinase; DPMQ = Dispensed Price for Maximum Quantity; IBR = ibrutinib; MBS = Medicare Benefits Schedule; MCL = mantle cell lymphoma; PBS = Pharmaceutical Benefits Scheme; RDI = relative dose intensity; R/R = relapsed/refractory.

[a] the submission presented the script ratio as 1.1; however, 1.06 is used in the BIM calculations.

6.76 The pre-PBAC response reiterated that the submission assumed market growth to follow the natural growth of the yearly increase in MCL incidence (4.2% per year) as reported in van Leeuwen et al. (2014), which estimated the average annual incidence of MCL in Australia. Analysis of script data for ibrutinib in R/R MCL (PBS item: 11419B) shows a 26.1% increase in scripts dispensed from 2019 (first full calendar year of listing) to 2020. The pre-PBAC response argued that the high initial increase in scripts can be attributed to the high initial uptake of ibrutinib, a superior therapy to

immunochemotherapy following PBS listing in August 2018, and that a continual growth rate of 26.1% per year was unlikely to eventuate considering the relatively low incidence of MCL.

6.77 Table 17 presents the estimated financial implications for the listing of acalabrutinib based on the cost-minimised price of acalabrutinib (DPMQ $[redacted]) and the published price of ibrutinib (DPMQ $11,672.21).

Table 17: Estimated use and financial implications (published DPMQ)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of acalabrutinib scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of ibrutinib scripts offset	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Estimated financial implications of acalabrutinib						
Cost to PBS/RPBS less copayments	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimated financial implications for ibrutinib						
Cost to PBS/RPBS less copayments	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to Government	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Tables 4.7, 4.11 & 4.13-4.15, pp126 & 128-130 of the submission.

DPMQ = Dispensed Price for Maximum Quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *$0 to < $10 million*

[3] *$10 million to < $20 million*

6.78 The total net cost to the PBS/RPBS of listing acalabrutinib was estimated to be $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, and a total of $0 to < $10 million over six years. The cost-minimised price of acalabrutinib included cost offsets for AEs avoided, resulting in a higher drug cost. The higher drug cost contributed to the net financial cost to the R/PBS.

6.79 The submission estimated that there would be fewer than < 500 grandfathered patients at the time of listing but assumed they would not result in an additional cost to the R/PBS. This may not be reasonable, however it is possible that the historical data used to determine the market size already accounts for at least some of the grandfathered patients (assuming they would have been treated with PBS-subsidised ibrutinib in the absence of acalabrutinib).

6.80 The following issues were identified with the estimates, although these may be managed through the Risk Share Arrangement (RSA):

- The submission stated that there is an unmet clinical need for an effective treatment for R/R MCL with fewer tolerability concerns. These currently untreated patients are not accounted for in the financial estimates.

- The submission requested PBS listing for patients with R/R MCL who have developed an intolerance to another BTK inhibitor requiring permanent treatment withdrawal. The financial estimates use a median treatment duration of 14.4 months, which included patients who discontinue early due to AEs. Patients who discontinue ibrutinib early and commence treatment with acalabrutinib would be in addition to those who commence ibrutinib/acalabrutinib as their first BTK inhibitor, which could increase the market size.
- Some grandfathered patients may have been excluded from the analysis (paragraph 6.79).
- Acalabrutinib uptake rate assumptions were not justified and may be underestimated.

6.81 The PBAC agreed with the DUSC that minor changes should be made to the methods used to derive the utilisation and financial estimates, and the structure of the estimates model. Specifically, the PBAC advised:

- The submission assumed no change in the relapsed and refractory (R/R) mantle cell lymphoma (MCL) market size. The proportion of patients previously untreated with BTK inhibitor due to relative contraindication were not included in the market share estimates. Newly eligible patients at risk of atrial fibrillation should be included in the estimated PBS usage of acalabrutinib.
- The submission assumed no change in the R/R market growth. There was a 26.1% increase in the number of ibrutinib scripts dispensed between 2019 and 2020, suggesting the steady state has not been reached. The pre-PBAC response provided data suggesting some stability of use in 2020. The PBAC considered that utilisation of ibrutinib should be based on an average growth over 2019 and 2020.
- The submission assumed equal length of treatment to ibrutinib. The trial based-median duration of treatment is more accurate as an estimate of time on treatment with acalabrutinib. The duration of acalabrutinib treatment should be adjusted to match the ACE-LY-004 trial (17.5 months).
- Grandfathered patients should be included.

Financial Management – Risk Sharing Arrangements

6.82 The submission proposed that uncertainties in market growth as well as other uncertainties associated with utilisation (Table 16) be addressed through the implementation of an appropriate RSA. The PBAC noted that risk sharing arrangements are currently in place for ibrutinib in MCL, and considered it would be appropriate for acalabrutinib to join the existing RSA without any revision to the expenditure caps. The PBAC noted that acalabrutinib may be used in patients contra-indicated for ibrutinib, but otherwise eligible, and that this may result in a small increase in overall use. However, noting its previous concern that the prevalent patient population informing the ibrutinib estimates were potentially overestimated

(paragraph 12.4, ibrutinib PSD, March 2018), the PBAC considered it would not be appropriate to revise the RSA caps without review of the actual utilisation for ibrutinib versus that expected.

Quality Use of Medicines

6.83 The DUSC noted that no QUM activities were proposed in the submission. DUSC noted the TGA Product Information which describes the recommended dose is 100 mg twice daily until disease progression. The dose may be increased to 200 mg twice daily if the patient is required to take a medicine that induces the CYP3A4 enzyme.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (immediate assessment) listing of acalabrutinib on the General Schedule for the treatment of relapsed or refractory (R/R) mantle cell lymphoma (MCL) who have received at least one prior therapy and have a WHO performance status of 0 or 1. Listing was recommended on a cost-minimisation basis against ibrutinib.

7.2 The PBAC considered that the equi-effective doses are acalabrutinib 100 mg twice daily for 17.5 months being equivalent to ibrutinib 560 mg once daily for 14.4 months.

7.3 The PBAC considered that a clinical need exists for alternative treatments in the proposed patient population because the existing option (ibrutinib) is associated with side effects. The PBAC noted the consumer comments received for this submission from health care professionals, which emphasised that acalabrutinib provides a meaningful response in patients, combined with better tolerability compared to the alternative BTK inhibitor, ibrutinib. The PBAC also noted the advice received from Lymphoma Australia, the Leukaemia Foundation, and Rare Cancers Australia which supported the proposed listing for acalabrutinib and was consistent with the evidence presented in the submission. The consumer comments from these organisations were not differentiated from those provided for zanubrutinib in R/R MCL.

7.4 Regarding the requested listing and restriction:

- The PBAC noted that the submission requested a listing for acalabrutinib that is consistent with the existing PBS listing for the comparator (ibrutinib) in MCL.
- The PBAC considered that the proposed criterion that would extend PBS listing to patients who commenced therapy with ibrutinib or another BTK inhibitor for the treatment of R/R MCL, and have not experienced disease progression, but develop an intolerance necessitating permanent treatment withdrawal, was appropriate. The PBAC recommended that an analogous criterion flow on to the restriction for ibrutinib in R/R MCL to ensure consistency with acalabrutinib (PBS Item 11419B).
- The PBAC noted that transitioning arrangements had been requested by the submission for a small number of patients (< 500) who will be treated under an early

access program and considered this appropriate, provided these patients are subject to same access criteria as those that will apply to the usual PBS population.

7.5 In terms of the clinical place for acalabrutinib, the PBAC agreed with the submission that acalabrutinib will be used as an alternative to ibrutinib and will be an option for patients contra-indicated or intolerant to ibrutinib.

7.6 The PBAC considered that the nomination of ibrutinib as the comparator was appropriate. The PBAC noted that while immunochemotherapy may also be considered a comparator, *Section 101(3B) of the National Health Act 1953* is satisfied because the PBAC has previously accepted that ibrutinib is superior to immunochemotherapy, and therefore it is also likely that acalabrutinib is superior to immunochemotherapy. The PBAC considered zanubrutinib a relevant near-market comparator.

7.7 The submission was based on one phase II, single-arm, open-label study of acalabrutinib (ACE-LY-004 [N=124]); one randomised, open-label, phase III trial comparing ibrutinib versus temsirolimus (MCL-3001/RAY [N= 139, ibrutinib arm]); and three phase II, single-arm, open-label studies of ibrutinib (PCYC-1104 [N=111], MCL-2001/SPARK [N=120] and MCL4001 [N=149]). The submission reported an analysis of the whole acalabrutinib trial populations, as well as two matching adjusted indirect comparisons (MAICs) of acalabrutinib and pooled ibrutinib studies. The submission presented whole trial (naïve) and MAIC analyses for ORR, best response, PFS and OS.

7.8 The PBAC acknowledged that the naïve comparison between acalabrutinib and ibrutinib was uncertain due to differences across the patient populations for the single arm studies. The PBAC also acknowledged the uncertainty associated with the unanchored MAICs that generated small effective sample sizes. Notwithstanding, the PBAC considered that both the naïve comparison and the MAIC analyses were consistent with non-inferiority and that on balance, acalabrutinib is likely to have similar effectiveness to ibrutinib in R/R MCL.

7.9 Regarding comparative harms, the PBAC noted that acalabrutinib appeared to be associated with less atrial fibrillation and thrombocytopenia, compared with ibrutinib. The PBAC noted that treatment discontinuations due to AEs were similar between acalabrutinib and ibrutinib (11.3% at 38.1 months in the ACE-LY-004 trial vs. 10.3% at 41.4 months in the pooled analysis of the MCL-3001/RAY, PCYC-1104 and MCL-2001/SPARK studies). Based on the evidence presented, the PBAC considered the submission's claim of non-inferior safety to be reasonable.

7.10 The cost-minimisation analysis, based on a claim of non-inferiority of acalabrutinib compared to ibrutinib, was accepted by the PBAC with changes to assumptions for treatment duration, AEs and RDIs as proposed by the ESC. The PBAC considered that the CMA should assume the median treatment durations from the latest data cut in each study, noting that despite the median follow-up being similar for both studies, the median duration of treatment was longer for acalabrutinib (17.5 months, at 38.1 months median follow up in the ACE-LY-004 trial) compared with ibrutinib (14.4

months, at 38.7 months median follow up in the MCL-3001/RAY study). The PBAC agreed with the ESC that to ensure the cost per patient treated with acalabrutinib is no more than for ibrutinib, the cost offsets for AEs and adjustments for RDIs should not be included in the CMA given the clinical uncertainty associated with the inputs informing these costs.

7.11 The PBAC considered the projected utilisation to be underestimated overall, however the financial impact to the Commonwealth will be limited because the effective price for acalabrutinib derived from the CMA reflects a price that will be cost neutral when ibrutinib is substituted. The PBAC advised that minor changes to the financial estimates model should include a duration of treatment to match the ACE-LY-004 trial and grandfathered patients. The PBAC noted that cost offsets due to AEs should not be included, and growth in the market should be estimated from ibrutinib utilisation data using an average over 2019 and 2020. The PBAC considered it would be appropriate for acalabrutinib to join the existing RSA for ibrutinib in MCL without any revision to the expenditure caps.

7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because acalabrutinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ibrutinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add indication (21449 – Mantle cell lymphoma) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
acalabrutinib 100 mg capsule, 56	12117R	1	56	5	Calquence

Restriction Summary [New 1] / Treatment of Concept [New 2]:		
Concept ID (for internal Dept. use)		**Category / Program:** GENERAL – General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required – immediate/real-time assessment (online/telephone)
Prescribing Rule Level	7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
	7608	**Administrative Advice:** Special Pricing Arrangements apply.
	New AA1	***Administrative Advice:*** *For the purposes of administering this restriction, current Bruton tyrosine kinase inhibitors are: acalabrutinib, ibrutinib, zanubrutinib [pending July 2021 PBAC outcome].*
	25796	**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.
21449		**Indication:** Mantle cell lymphoma
		Treatment Phase: Initial treatment
17702		**Clinical criteria:**
21191		The condition must have relapsed or be refractory to at least one prior therapy.
		AND
10859		**Clinical criteria:**
10858		Patient must have a WHO performance status of 0 or 1.
		AND
7890		**Clinical criteria:**
7889		The treatment must be the sole PBS-subsidised therapy for this condition.
		AND
		Clinical criteria:
New CC1		Patient must be untreated with Bruton tyrosine kinase inhibitor therapy; or
New CC2		Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication.
Restriction Summary [New 3] / ToC [New 4]:		
21449		**Indication:** Mantle cell lymphoma
		Treatment Phase: Continuing treatment
7890		**Clinical criteria:**
7889		The treatment must be the sole PBS-subsidised therapy for this condition.
		AND
11365		**Clinical criteria:**
11364		Patient must have previously received PBS-subsidised treatment with this drug for this condition.
		AND
		Clinical criteria:
23678		Patient must not have developed disease progression while being treated with this drug for this condition.
Restriction Summary [New 5] / ToC [New 6]:		

21449	**Indication:** Mantle cell lymphoma
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	Clinical criteria:
New CC3	Patient must have received treatment with this drug prior to [insert listing date here].
	AND
25394	**Clinical criteria:**
25393	The condition must have relapsed or be refractory to at least one prior therapy prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	AND
21830	**Clinical criteria:**
21831	Patient must have had a WHO performance status of 0 or 1 at the time non-PBS-subsidised treatment with this drug for this condition was initiated.
	AND
7890	**Clinical criteria:**
7889	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
New GFCC1	Patient must have been untreated with Bruton tyrosine kinase inhibitor therapy at treatment initiation with this drug; or
New CC2	Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication.
	AND
	Clinical criteria:
23678	Patient must not have developed disease progression while being treated with this drug for this condition.
17098	**Administrative advice:** Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
25398	**Administrative advice:** This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

8.2 Flow on changes to ibrutinib's current Mantle cell lymphoma restrictions, to permit ibrutinib use following acalabrutinib intolerance, are summarised as follows:

Concept ID (for internal Dept. use)	**MEDICINAL PRODUCT / medicinal product pack:** IBRUTINIB / ibrutinib 140 mg capsule, 120
	PBS item code: 11419B
	Restriction summary: 10834 *(as at 1 July 2021; only relevant edits displayed below)* - update to form New 1
	Indication: 21449 – Mantle cell lymphoma
	Treatment phase: Initial treatment
14393	**Clinical criteria:**
Remove 14392	~~Patient must not have previously received PBS-subsidised treatment with this drug for this condition~~
Insert New CC1	*Patient must be untreated with Bruton tyrosine kinase inhibitor therapy; or*
Insert New CC2	*Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication.*
Insert New AA1	***Administrative Advice:*** *For the purposes of administering this restriction, current Bruton tyrosine kinase inhibitors are: acalabrutinib, ibrutinib, zanubrutinib [pending July 2021 PBAC outcome].*
Editorial change	**Restriction summary:** 10898 *(current as at 1 July 2021; only relevant edits shown;)* – update to form New 3
	Treatment Phase: Continuing treatment
21104	**Clinical criteria:**
Remove 21103	~~Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition~~
Insert 23678	Patient must not have developed disease progression while being treated with this drug for this condition.

***This restriction 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.