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

1 Purpose of submission

1.1 The submission requested a Section 85 (General Schedule), Authority Required (Telephone/Streamlined) listing for acalabrutinib for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL)/small lymphocytic leukaemia (SLL) considered unsuitable for treatment or retreatment with a purine analogue.

1.2 Listing was requested on the basis of a cost-minimisation analysis versus ibrutinib.

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

Component	Description
Population	Patients with relapsed/refractory CLL or SLL considered unsuitable for treatment or retreatment with a purine analogue.
Intervention	Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity.
Comparator	- Oral ibrutinib 420 mg daily until disease progression or unacceptable toxicity. - Oral venetoclax 400 mg daily (following completion of a 5-week dose titration) until disease progression, unacceptable toxicity or a maximum of 24-months; intravenous rituximab every 28 days for six cycles.
Outcomes	Progression-free survival, overall survival, overall response rate, safety.
Clinical claim	- Acalabrutinib is non-inferior to ibrutinib for the outcomes of progression-free survival and overall survival, and superior in terms of adverse events. - The submission did not include an explicit clinical claim versus venetoclax plus rituximab.

Source: Table 1.1.1, p.7 of the submission.
Abbreviations: CLL, chronic lymphocytic anaemia; SLL, small lymphocytic lymphoma.

2 Background

Registration status

2.1 Acalabrutinib was TGA registered on 21 November 2019 for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). Acalabrutinib is also indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

2.2 The submission stated that a concurrent submission has been submitted to the April 2020 MSAC meeting requesting the addition of acalabrutinib to MBS Item 73343 (detection of 17p chromosomal deletions by fluorescence in situ hybridisation (FISH) in a patient with R/R CLL/SLL), for the purpose of assessing PBS eligibility for acalabrutinib treatment.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
ACALABRUTINIB acalabrutinib 100 mg capsule, 56	1	56	5	$[redacted]	Calquence®	AstraZeneca Australia Pty Ltd

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction level/Method:	☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Authority Required - Streamlined
Episodicity:	*Relapsed or refractory*
Condition:	~~C~~chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication:	~~Treatment or retreatment of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)~~ *Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)*
Treatment phase:	Initial *treatment*
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have relapsed or be refractory to at least one prior therapy AND Patient must have a WHO performance status of ~~less than or equal to 2~~ *0 or 1* *AND* *Patient must not have previously received PBS-subsidised treatment with this drug for this condition* AND Patient must not have ~~previously~~ received ~~PBS-subsidised~~ treatment with another *Bruton's tyrosine kinase (*BTK*)* inhibitor *for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease);* 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 CLL/SLL* AND Patient must be considered unsuitable for treatment or retreatment with a purine analogue
Prescribing instructions:	A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following: a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles; b) Age is 70 years or older; c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen; d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia; e) Evidence of one or more 17p chromosomal deletions demonstrated by fluorescence in situ hybridisation (FISH)
Administrative advice:	*No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

Category/Program:	GENERAL – General Schedule (Code GE)

Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction level/Method:	☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing ☒*Authority Required – Telephone/Electronic/Emergency* ☒~~Authority Required - Streamlined~~
Episodicity:	*Relapsed or refractory*
Condition:	~~C~~chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication:	~~Treatment or retreatment of~~ chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase:	Continuing *treatment of relapsed or refractory CLL/SLL*
Clinical criteria	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
Administrative advice:	*No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

Category/Program:	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐*Dental* ☒*Medical Practitioners* ☐*Nurse practitioners* ☐*Optometrists* ☐*Midwives*
Restriction level/Method:	☐*Unrestricted benefit* ☐*Restricted benefit* ☐*Authority Required – In Writing* ☒*Authority Required – Telephone/Electronic/Emergency* ☐*Authority Required - Streamlined*
Episodicity:	*Relapsed or refractory*
Condition:	*chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)*
Indication:	*Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)*
Treatment phase:	*Grandfathering treatment (initial treatment in a patient commenced on non-PBS subsidised treatment)*
Clinical criteria:	*Patient must have previously received non-PBS-subsidised treatment with this drug for relapsed or refractory CLL/SLL prior to 1 Month 202X [insert listing date here]* *AND* *The treatment must be the sole PBS-subsidised therapy for this condition* *AND* *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* *Patient must have had a WHO performance status of ~~2 or less~~ 0 or 1 prior to initiating non-PBS subsidised treatment with this drug for this condition* *AND* *Patient must have been considered unsuitable for treatment or retreatment with a purine analogue prior to initiating non-PBS subsidised treatment with this drug for this condition* *AND* *Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease) prior to initiating non-PBS subsidised treatment with this drug for this condition; 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 CLL/SLL prior to initiating non-PBS subsidised treatment with this drug for this condition* *AND* Patient must be considered unsuitable for treatment or retreatment with a purine analogue AND *Patient must not have developed disease progression while receiving treatment with this drug for this condition*
Prescribing instructions:	***Prescribing Instructions:*** *A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:*

	a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles; *b) Age is 70 years or older;* *c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;* *d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;* *e) Evidence of one or more 17p chromosomal deletions demonstrated by fluorescence in situ hybridisation (FISH)*
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.* *This grandfathering restriction will cease to operate from [insert date 12 months from listing date here]* *No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

3.2 The submission noted that ibrutinib is subject to a Special Pricing Arrangement (SPA) and requested a SPA to match the ibrutinib effective price.

3.3 The requested published Dispensed Price for Maximum Quantity (DPMQ) of $[redacted] is higher than the DPMQ derived in the cost-minimisation analysis ($[redacted]), which was based on the published price of ibrutinib.

3.4 The submission stated that the proposed restriction was based on the current ibrutinib R/R CLL/SLL restriction. The differences noted include:

- Broadening of the allowed WHO performance status from ≤ 1 to ≤ 2 to align with the inclusion criteria of the key trial, ASCEND;
- Removal of the criterion specifying that a patient must not have previously received PBS-subsidised treatment with this drug for this condition, and replacement with a criterion specifying that a patient must not have previously received PBS-subsidised treatment with "another" Bruton's tyrosine kinase (BTK) inhibitor. This does not explicitly prevent retreatment with acalabrutinib.
- Inclusion of a criterion permitting use of acalabrutinib among patients who have developed intolerance to another BTK inhibitor of a severity necessitating permanent treatment withdrawal.

3.5 The PBAC considered that, although the key acalabrutinib trial recruited patients with a WHO performance status ≤ 2, in order to align the acalabrutinib and ibrutinib patient populations, the proposed acalabrutinib restriction should restrict use to patients with a WHO performance status of ≤ 1.

3.6 The proposed criteria specifying suitability for treatment/retreatment with a purine analogue are identical to the criteria included in the ibrutinib restriction. However, this is narrower than the population in the ASCEND trial, which did not exclude patients on the basis of purine analogue suitability.

3.7 Under the proposed restriction, patients who have developed intolerance to ibrutinib would be eligible for treatment with acalabrutinib. There is currently limited available clinical evidence assessing treatment outcomes among patients with ibrutinib intolerance who are subsequently treated with acalabrutinib. The Pre-Sub-Committee response (PSCR) stated that new data from an unpublished trial ACE-CL-001 (Phase 1/2, open-label, N=33) demonstrates that treatment of ibrutinib intolerant patients with acalabrutinib results in efficacy benefits. Among the 25 responders in the study, the median duration of response was not reached. The ESC considered the proposed restriction criteria was appropriate and allows patients who are intolerant to ibrutinib to receive treatment with acalabrutinib which, although having the same mechanism of action, has a different adverse event profile.

3.8 The submission requested an Authority Required (Streamlined) listing for continuing treatment of acalabrutinib. This differed from the requested initial treatment restriction and the authority level for the continuing ibrutinib PBS listing which are Authority Required (Telephone). The PBAC agreed with ESC and considered that the authority level for continuing treatment with acalabrutinib should be consistent with the PBS listing of ibrutinib (Authority Required (Telephone)).

3.9 The submission requested grandfathering provisions for approximately < 500 patients who will be treated under the sponsor's compassionate access program. The Secretariat proposed wording for a grandfather listing in line with the requirements contained in the initial treatment restriction, but with the added requirement that grandfathered patients must have not developed disease progression.

3.10 The PBAC considered that the current initial treatment ibrutinib listing for R/R CLL/SLL would require flow-on changes to ensure patients have not previously received PBS-subsidised treatment with another BTK inhibitor unless intolerant.

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

4 Population and disease

4.1 CLL is characterised by the progressive accumulation of functionally incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, spleen and liver. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating and unintentional weight loss. SLL is a different manifestation of the same disease. In CLL, abnormal lymphocytes are predominantly found in blood, bone marrow and lymphoid tissue, whereas in SLL, abnormal lymphocytes are predominantly located in lymph nodes, bone marrow and other lymphoid tissue.

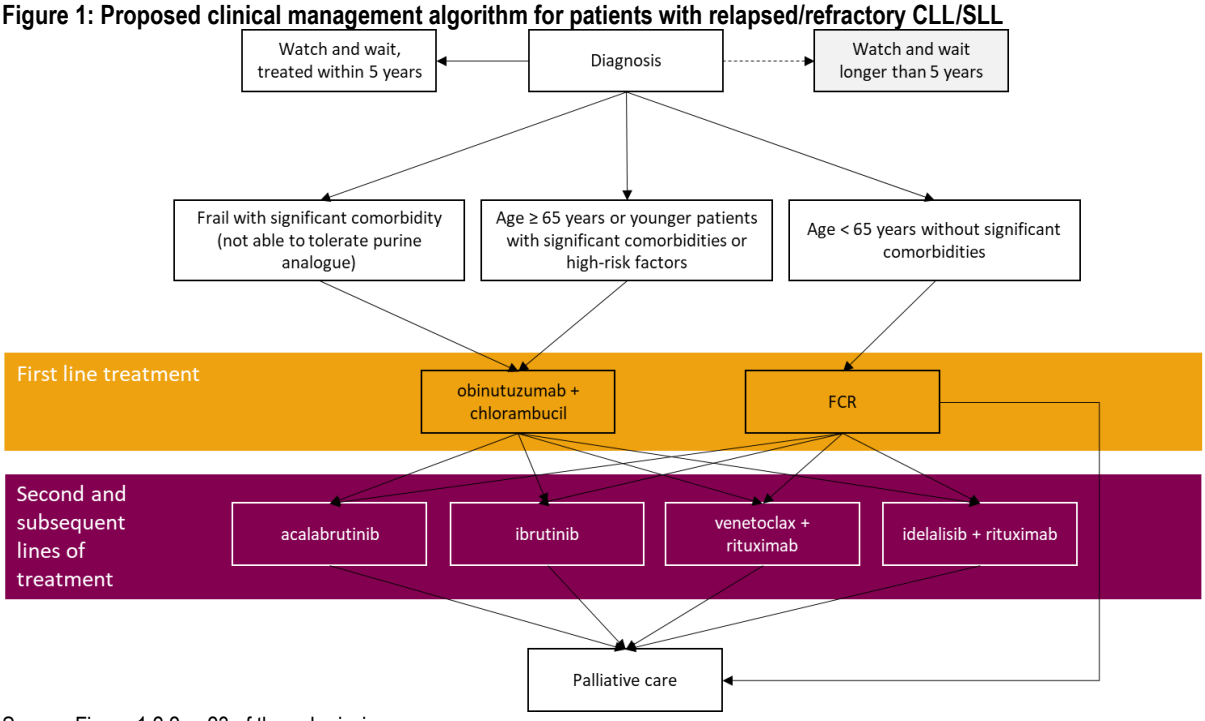
4.2 CLL/SLL is more common in men than women (65% versus 35%), with a mean age at diagnosis in Australia of 70 years (males 68.8 years, females 71.2 years). Characteristics associated with a worse prognosis include genetic factors (17p deletion/TP53 mutation, 11q deletion, unmutated IGHV), biochemical/cell surface markers (serum thymidine kinase, serum β_2 microglobulin, CD49d/CD38 positivity,

ZAP-70 positivity), and patient characteristics (male sex, older age, worse Eastern Cooperative Oncology Group (ECOG) performance score).

4.3 CLL/SLL is generally a slowly progressing cancer, with many patients managed with a 'watch and wait' approach until symptoms develop. A proportion of patients never require treatment. The choice of therapy depends on a number of factors, including age, fitness, comorbidities, and the presence of prognostic genetic mutations. Treatment is typically non-curative, with patients potentially receiving multiple lines of therapy as their disease becomes relapsed/refractory to their current treatment.

4.4 Figure 1 below presents the proposed clinical management algorithm presented in the submission. The algorithm positions acalabrutinib as a second/subsequent-line option for the treatment of CLL/SLL, along with ibrutinib, venetoclax plus rituximab, and idelalisib plus rituximab.

Figure 1: Proposed clinical management algorithm for patients with relapsed/refractory CLL/SLL



Source: Figure 1.2.2, p.23 of the submission.
Abbreviations: FCR, fludarabine + cyclophosphamide + rituximab.

5 Comparator

5.1 The submission nominated ibrutinib monotherapy as the main comparator. The main arguments provided in support of this comparator were:

- ibrutinib is PBS-listed for the treatment of patients with R/R CLL/SLL who are unsuitable for treatment with a purine analogue, and ibrutinib belongs to the same therapeutic class as acalabrutinib (BTK inhibitors); and

- based on the results of a 10% Medicare sample analysis commissioned by the sponsor, treatment of R/R CLL/SLL patients who are unsuitable for treatment with a purine analogue is predominantly with ibrutinib.

5.2 The following additional PBS-listed medicines may be considered as alternate comparators as they could be replaced in practice: venetoclax plus rituximab, idelalisib plus rituximab, and chemo-immunotherapy combinations. Some of these alternative therapies may be less costly than acalabrutinib.

5.3 Venetoclax plus rituximab is also PBS-listed for use in the requested population, but is used to a lesser extent than ibrutinib. A supplementary comparison of acalabrutinib and venetoclax plus rituximab was included in the submission.

5.4 Idelalisib plus rituximab is also PBS-listed in an overlapping population (patients with R/R CLL/SLL and a Cumulative Illness Rating Scale score of > 6 who are considered unsuitable for chemo-immunotherapy). Comparative evidence for acalabrutinib versus idelalisib plus rituximab was included in the submission, as the comparator arm of the ASCEND trial was investigator's choice of either idelalisib plus rituximab (received by 77% of patients), or bendamustine plus rituximab. The ESC and considered that idelalisib plus rituximab was not an appropriate comparator as it is not widely used in the second line setting due to lower efficacy and higher toxicity than other available options. The ESC noted that data from the ASCEND trial indicated that acalabrutinib had improved progression free survival compared to idelalisib plus rituximab, or bendamustine plus rituximab (HR = 0.31; 95% CI: 0.20, 0.49) and fewer treatment related adverse events (65.6% versus 94.1%). The ESC noted that bendamustine is not available on the PBS for this indication.

5.5 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. The PBAC noted, based on the results of the ASCEND trial, that acalabrutinib resulted in superior progression free survival outcomes and a superior safety profile compared to idelalisib plus rituximab.

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 individuals (9) and organisations (3) via the Consumer Comments facility on the PBS website. The individuals' comments

described a range of benefits of treatment with acalabrutinib including potentially fewer side effects and avoidance of toxicity in place of other therapies, improving quality of life, especially for elderly patients. The PBAC noted that this advice was supportive of the evidence provided in the submission, although there was uncertainty surrounding the comparative safety benefits compared to the comparator, ibrutinib.

6.3 The PBAC noted the advice received from Lymphoma Australia, Leukaemia Foundation and Rare Cancers Australia. The PBAC considered that the advice offered by the key organisations provided little additional insight into the need for acalabrutinib.

Clinical trials

6.4 No head-to-head trials comparing acalabrutinib to ibrutinib or to venetoclax plus rituximab were identified in the literature search.

6.5 The submission was based on the following comparisons of acalabrutinib and the nominated comparators:

- An unanchored matching adjusted indirect comparison (MAIC) of acalabrutinib (ASCEND) and ibrutinib (RESONATE);
- A Bucher method indirect comparison of acalabrutinib (ASCEND) versus ibrutinib plus bendamustine plus rituximab (HELIOS) using investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab (ASCEND), and placebo plus bendamustine plus rituximab (HELIOS) as common reference;
- An unanchored MAIC of acalabrutinib (ASCEND) and venetoclax plus rituximab (MURANO);
- A Bucher method indirect comparison of acalabrutinib (ASCEND) versus venetoclax plus rituximab (MURANO) using investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab (ASCEND), and bendamustine plus rituximab (MURANO) as common reference.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Acalabrutinib trials		
ASCEND NCT02970318	A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia.	Clinical Study Report 17 July 2019.
Ibrutinib trials		
RESONATE NCT01578707	Byrd JC, Brown JR, O'Brien S et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.	New England Journal of Medicine 2014; 371(3): 213-23.
	Brown JR, Hillmen P, O'Brien S, et al. Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATE Trial of Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.	Blood 2014; 124(21): 3331.
	Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL.	Blood 2017; 129(19): 2612-2615.
	Barrientos JC, O'Brien S, Brown JR, et al. Improvement in Parameters of Hematologic and Immunologic Function and Patient Well-being in the Phase III RESONATE Study of Ibrutinib Versus Ofatumumab in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.	Clinical Lymphoma, Myeloma & Leukemia 2018; 18(12): 803-813.e7.
	Brown JR, Hillmen P, O'Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL.	Leukemia 2018; 32(1): 83-91.
	Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab.	Blood 2019; 133(19): 2031-2042.
	Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma.	American Journal of Hematology 2019; 94: 1353-1363.
HELIOS NCT01611090	Hallek M, Kay NE, Osterborg A, et al. The HELIOS trial protocol: a phase III study of ibrutinib in combination with bendamustine and rituximab in relapsed/refractory chronic lymphocytic leukemia.	Future Oncology 2015; 11(1): 51-9.
	Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study.	The Lancet 2016; Oncology. 17 (2): 200-211.
	Cramer P, Fraser G, Santucci-Silva R, et al. Improvement of fatigue, physical functioning, and well-being among patients with severe impairment at baseline receiving ibrutinib in combination with bendamustine and rituximab for relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma in the HELIOS study.	Leukemia & Lymphoma 2018; 59(9): 2075-2084.
	Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma.	Leukemia 2019; 33(4): 969-980.

Trial ID	Protocol title/ Publication title	Publication citation
Venetoclax plus rituximab trials		
MURANO NCT02005471	Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. Kater AP, Seymour JF, Hillmen PH, et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukaemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study.	New England Journal of Medicine 2018; 378(12): 1107-1120. Journal of Clinical Oncology 2019; 37(4): 269-277.

Source: Table 2.2.1, pp36-38 of the submission.

6.7 The key features of the included trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/duration of follow-up	Risk of bias	Patient population	Outcomes
Acalabrutinib vs. investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab					
ASCEND	310	Phase 3, R, OL (median duration of follow-up 16 months)	Unclear	-Adult patients with CD20-positive CLL; -≥ 1 prior CLL therapy; -ECOG ≤ 2.	-IRC-assessed PFS (primary) -Investigator-assessed PFS -IRC- and investigator-assessed overall response -OS -Proportion with MRD negative CR -HRQOL (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue).
Ibrutinib vs. ofatumumab					
RESONATE	391	Phase 3, R, OL (median duration of follow-up 65 months)	Unclear	-Adult patients considered inappropriate for purine analogue-based treatment; -≥ 1 prior CLL therapy; -ECOG ≤ 1.	-IRC-assessed PFS (primary) -Investigator-assessed PFS -IRC- and INV-assessed ORR -OS -Proportion with MRD negative CR -HRQOL (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue).
Ibrutinib plus bendamustine plus rituximab vs. placebo plus bendamustine plus rituximab					
HELIOS	578	Phase 3, R, DB, PC (median duration of follow-up 35 months)	Low	-Adult patients with relapsed or refractory CLL or SLL; -≥ 1 prior CLL therapy; -ECOG score ≤ 1; -Measurable lymph node disease (> 1.5 cm) by CT scan. -Excluded patients with 17p deletion.	-IRC-assessed PFS (primary) -INV-assessed PFS -IRC- and INV-assessed ORR -OS -Proportion with MRD negative CR -HRQOL (time to improvement in FACIT-Fatigue)
Venetoclax plus rituximab vs. bendamustine plus rituximab					
MURANO	389	Phase 3, R, OL (median duration of follow-up 36 months)	Unclear	-Adult patients with relapsed or refractory CLL; -1 to 3 prior lines of therapy, including at least one standard chemotherapy-containing regimen; -ECOG score ≤ 1.	-INV-assessed PFS (primary) -IRC-assessed PFS -INV-assessed best OR -IRC- and INV-assessed response -OS -Event-free survival -Proportion with MRD negativity at assessment time points -HRQOL (MDASI, EORTC QLQ-C30 and QLQ-CLL16)

Source: Table 2.4.3, pp60-64; Section 2.4.2 pp57-58 of the submission; Table 5.4.3, pp9-11 of 'Appendix 1_supplementary analyses'; Section 9.3, pp54-60 of the ASCEND CSR; p.3 of Chanan-Khan et al. (2016); pp53-55 of the MURANO trial protocol (Seymour et al., 2018); pp9-10 of the RESONATE trial protocol (Byrd et al., 2014).

Abbreviations: CD, cluster of differentiation; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol 5-Dimension; FACIT, Functional Assessment of Chronic Illness Therapy; HRQOL, health-related quality of life; IRC, independent review committee; MDASI, M.D. Anderson Symptom Inventory; OL, open-label; OS, overall survival; PFS, progression-free survival; QLQ, Quality of Life Questionnaire; R, randomised; SLL, small lymphocytic lymphoma.

6.8 The ASCEND, RESONATE and MURANO trials had an unclear risk of bias. As the trials were open label, investigators, patients, and study personnel were not blinded to treatment allocation. Assessments made by study investigators were at high risk of bias. However, each trial included blinded assessments by an independent review committee, which offered a lower risk of bias.

6.9 The HELIOS trial had a low risk of bias as the investigators, patients, and study personnel were blinded to treatment assignment, and the ibrutinib and placebo capsules were identical in appearance. However, the HELIOS trial was unblinded after the interim analysis, and therefore, longer-term results were at a higher risk of bias.

6.10 All trials recruited adult patients who had received at least one prior therapy. There were differences across the trials in terms of eligibility criteria and baseline characteristics, including the median patient age, proportion of male patients, number of prior therapies, median time since last therapy, disease stage, ECOG score, proportion with bulky disease and the proportion with prognostic mutations; however, the ESC considered that these differences were not significant.

6.11 Patients in the RESONATE trial were inappropriate for treatment with a purine analogue and at a more advanced disease stage, compared to patients in the ASCEND trial. The ASCEND trial recruited patients with an ECOG performance status of ≤ 2, whereas the RESONATE, HELIOS and MURANO trials recruited patients with an ECOG of ≤ 1. The ESC noted the HELIOS trial excluded patients with 17p deletion, which is the poorest prognostic group. The ASCEND and MURANO trials recruited patients with CLL only, whereas the HELIOS and RESONATE trials recruited patients with CLL or SLL. The ESC considered that this was not a clinically significant difference.

6.12 There were differences between the trials in the planned treatment durations. In the MURANO trial, venetoclax was administered up to a maximum of 24 months, compared to acalabrutinib and ibrutinib in the ASCEND, RESONATE and HELIOS trials, which were administered until disease progression or unacceptable toxicity.

6.13 The ASCEND, RESONATE and HELIOS trials allowed patients in the comparator arms to cross over to receive treatment with acalabrutinib/ibrutinib in the case of disease progression. Crossover was not permitted in the MURANO trial. Overall survival results are likely to have been affected by patient crossover and the use of other therapies in the post-progression setting.

6.14 Non-inferiority margins were not nominated in the submission. 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 progression-free survival, overall survival, overall response, or time to next treatment in this disease area. The PSCR noted that the PBAC submission for venetoclax plus rituximab, which received a positive recommendation in November 2018, did not nominate a non-inferiority margin. The ESC considered that the lack of a statistically significant difference may not be sufficient to establish non-inferiority.

6.15 The PSCR added that a phase 3, randomised, open-label, non-inferiority head-to-head study (NCT02477696) of acalabrutinib versus ibrutinib in patients with previously treated high risk CLL, is currently being conducted. The ESC noted that preliminary data is expected to be available in the fourth quarter of 2021. The ESC considered that,

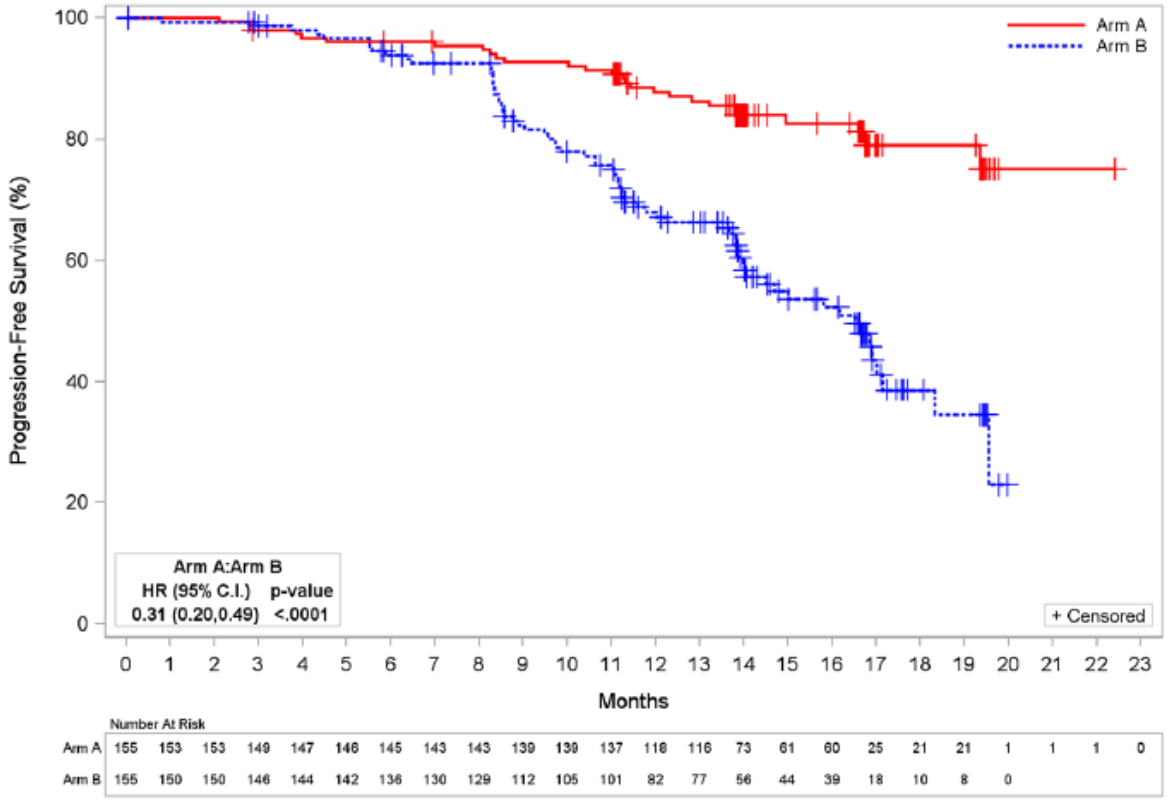
due to the relatively slow progression of the disease it may be several years (e.g. 3–5 years) before any significant data are generated.

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

Comparative effectiveness

6.16 Figure 2 presents the Kaplan-Meier plot of independent review committee-assessed progression-free survival for the ASCEND trial at the interim analysis.

Figure 2: Kaplan-Meier plot of independent review committee-assessed progression-free survival for the ASCEND trial at the interim analysis



Source: Figure 2.5.1, p.66 of the submission.
Abbreviations: CI, confidence interval; HR, hazard ratio.
Arm A: Acalabrutinib; Arm B: Investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab.

6.17 Table 4 presents the results for independent review committee and investigator-assessed progression-free survival for the ASCEND trial at the interim analysis.

Table 4: Progression-free survival results for the ASCEND trial at the interim analysis

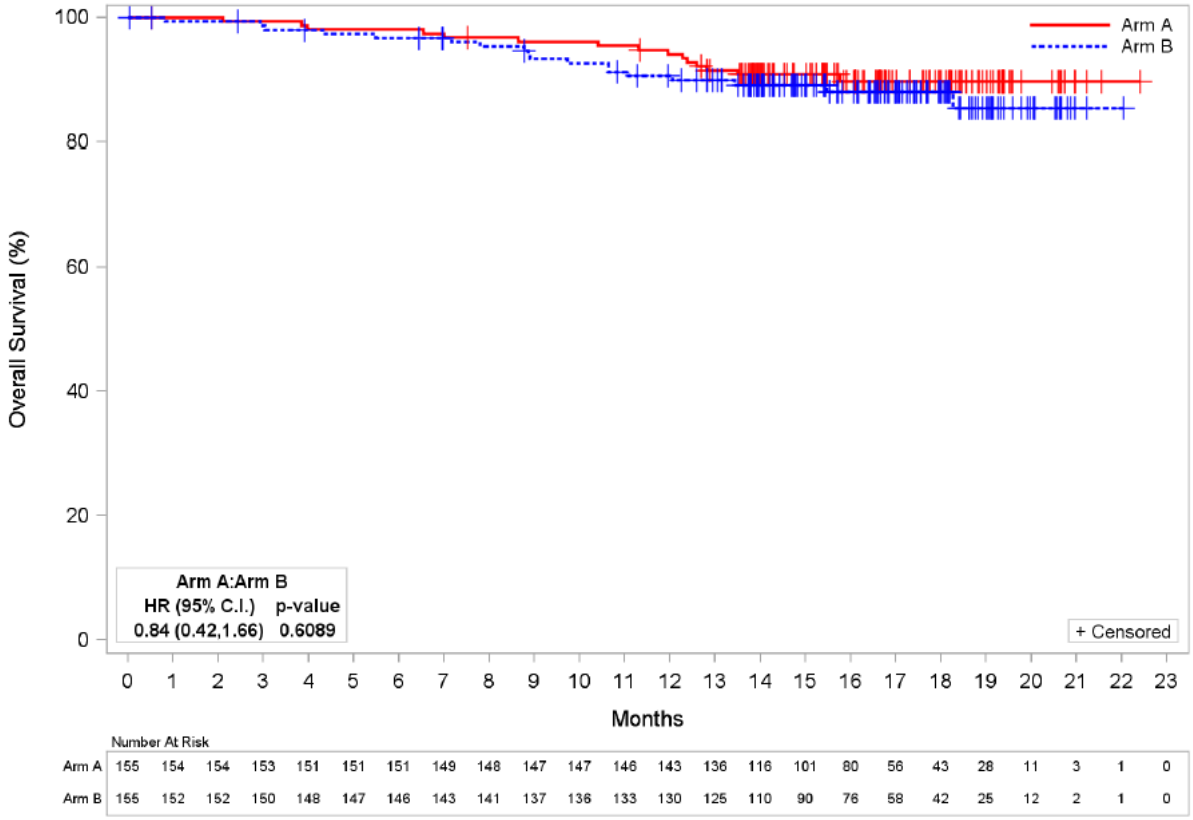
Cohort	ACAL (N=155)	IDEL/BEN + RITU (N=155)
Median duration of follow-up, months (range)	16.10 (0.53, 22.41)	15.75 (0.03, 22.05)
Independent review committee-assessed (primary outcome)		
Earliest event total, n (%) - Progression, n - Death, n	27 (17.4) 19 8	68 (43.9) 59 9
Median PFS, months (95% CI)	Not reached (NE)	16.5 (14.0, 17.1)
Within trial HR (95% CI)	0.31 (0.20, 0.49)	
KM estimate of PFS - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI)	 96.1 (91.5, 98.2) 87.8 (81.3, 92.1) 79.0 (69.7, 85.8)	 93.9 (88.6, 96.8) 68.0 (59.4, 75.1) 38.6 (27.3, 49.8)
Investigator-assessed		
Earliest event total, n (%) - Progression, n - Death, n	24 (15.5) 17 7	68 (43.9) 58 10
Median PFS, months (95% CI)	Not reached (NE)	16.2 (14.0, NE)
Within trial HR (95% CI)	0.28 (0.18, 0.45)	
KM estimate of PFS - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI)	 94.1 (89.0, 96.9) 88.7 (82.4, 92.8) 82.8 (74.6, 88.5)	 92.7 (87.2, 95.9) 67.4 (59.1, 74.4) 43.9 (33.4, 53.8)

Source: Table 18, pp113-114; Table 20, p.121 of the ASCEND clinical study report.
Abbreviations: ACAL, acalabrutinib; BEN, bendamustine; CI, confidence interval; HR, hazard ratio; IDEL, idelalisib; KM, Kaplan-Meier; NE, not estimable; PFS, progression-free survival; RITU, rituximab.

6.18 At a median duration of follow-up of 16 months, independent review committee-assessed progression-free survival was statistically significantly longer among patients in the acalabrutinib arm compared to the bendamustine/idelalisib plus rituximab arm (median not reached versus 16.5 months; HR = 0.31; 95% CI: 0.20, 0.49). Results based on investigator assessment were consistent with the independent review committee-assessed results (median not reached versus 16.2 months; HR = 0.28; 95% CI: 0.18, 0.45).

6.19 Figure 3 presents the Kaplan-Meier plot of overall survival for the ASCEND trial at the interim analysis.

Figure 3: Kaplan-Meier plot of overall survival for the ASCEND trial at the interim analysis



Source: Figure 2.5.5, 71 of the submission.
Abbreviations: CI, confidence interval; HR, hazard ratio.
Arm A: Acalabrutinib; Arm B: Investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab.

6.20 Table 5 presents the results for overall survival for the ASCEND trial at the interim analysis.

Table 5: Overall survival results for the ASCEND trial at the interim analysis

Cohort	ACAL (N=155)	IDEL/BEN + RIT (N=155)
Median duration of follow-up, months (range)	16.10 (0.53, 22.41)	15.75 (0.03, 22.05)
Death, n (%)	15 (9.7)	18 (11.6)
Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)
Within trial HR (95% CI)	0.84 (0.42, 1.66)	
KM estimate of OS - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI) - 21 months, % (95% CI)	 98.1 (94.1, 99.4) 94.1 (89.0, 96.9) 89.7 (83.4, 93.7) 89.7 (83.4, 93.7)	 96.7 (92.3, 98.6) 90.6 (84.6, 94.3) 88.1 (81.4, 92.5) 85.5 (76.4, 91.3)

Source: Table 25, p.131 of the ASCEND clinical study report.
Abbreviations: ACAL, acalabrutinib; BEN, bendamustine; CI, confidence interval; HR, hazard ratio; IDEL, idelalisib; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; RITU, rituximab.

6.21 At a median duration of follow-up of 16 months, median overall survival was not reached for acalabrutinib or idelalisib/bendamustine plus rituximab, and there was no statistically significant difference between the treatment arms. Low numbers of events in each arm indicate that the overall survival results are immature.

6.22 There were no statistically significant differences between treatment arms for the change from baseline to Week 24 or 48 in the FACIT-Fatigue global fatigue score, fatigue symptom score, or fatigue impact score.

6.23 There were no statistically significant differences between treatment arms for the change from baseline to Week 48 for any of the EORTC QLQ-C30 domain scores. Statistically significant differences favouring the idelalisib/bendamustine plus rituximab arm for the change from baseline to Week 24 were noted in the physical functioning, emotional functioning, cognitive functioning and pain domains.

6.24 Both treatment arms showed small improvements (< 3 points) in EQ-5D visual analogue scale scores, although there were no statistically significant differences. Results for the change from baseline in EQ-5D-5L overall scores were not available.

Matching adjusted indirect comparisons (MAIC)

6.25 The submission presented the results of two unanchored MAICs:

- A comparison of acalabrutinib versus ibrutinib based on individual patient data from the ASCEND trial and published data for the RESONATE trial;
- A comparison of acalabrutinib versus venetoclax plus rituximab based on individual patient data from the ASCEND trial and published data for the MURANO trial.

6.26 For an unanchored MAIC, population adjustment methods should adjust for all effect modifiers and prognostic variables in order to reliably predict absolute outcomes. Failure to adjust for all prognostic and effect modifier variables leads to an unknown amount of bias in the unanchored estimate (Phillippo et al., 2018).

6.27 There was minimal detail provided in the submission regarding the determination of prognostic and treatment effect modifier variables and therefore, it was unclear whether they were all identified in the analysis. The matching was constrained by the availability of published patient characteristics for the RESONATE and MURANO trials. The choice of cut-offs used for some of the included dichotomous variables was not adequately justified, and may not have adequately captured the differences between the trials. The PSCR stated that the prognostic factors were identified from published review of the literature and input from two clinical experts; and that the cut-off choices were determined based on published data available for ibrutinib and venetoclax. The ESC considered it was unknown if all the relevant prognostic and treatment variables were identified and matched.

MAIC of acalabrutinib versus ibrutinib

6.28 In order to match the inclusion criteria for RESONATE, which recruited patients with an ECOG ≤ 1, patients in the acalabrutinib arm of ASCEND who had an ECOG of 2 at baseline (n=19) were excluded. A further four patients were excluded due to missing data, leaving 132 patients available for matching.

6.29 Table 6 presents the prognostic and treatment effect modifier variables chosen for matching, along with the proportion of patients in the acalabrutinib arm before and after matching.

Table 6: Distribution of effect modifiers and prognostic variables before and after re-weighting for the MAIC of acalabrutinib and ibrutinib

Effect modifier and prognostic characteristics	ACAL unadjusted (N=132)[1]	IBR (N=195)	*p*-value for difference	ACAL MAIC adjusted (N=44)[2]
Age ≥70, n (%)	48 (36.4%)	78 (40.0%)	0.58	40.0%
Male, n (%)	94 (71.2%)	129 (66.0%)	0.38	66.0%
Bulky disease <5 cm, n (%)	66 (50.0%)	124 (64.0%)	<0.05	64.0%
17p deletion, n (%)	25 (18.9%)	63 (32.0%)	<0.01	32.0%
11q deletion, n (%)	30 (22.7%)	63 (32.0%)	0.09	32.0%
ECOG score = 0, n (%)	57 (43.2%)	79 (41.0%)	0.78	41.0%
ECOG score = 1, n (%)	75 (57.0%)	116 (59.0%)	0.93	59.0%
β_2-microglobulin >3.5 mg/L, n (%)	108 (81.8%)	153 (78.0%)	0.48	78.0%
Rai stage 0-2, n (%)	78 (59.1%)	86 (44.0%)	1.03	44.0%
Rai stage 3-4, n (%)	54 (40.9%)	109 (56.0%)	<0.01	56.0%
Prior treatments = 1, n (%)	68 (51.5%)	35 (18.0%)	<0.0001	18.0%
Prior treatments = 2, n (%)	36 (27.3%)	57 (29.0%)	0.83	29.0%
Prior treatments ≥3, n (%)	13 (9.8%)	103 (53.0%)	<0.0001	53.0%
Complex karyotype, n (%)	40 (30.3%)	49 (25.0%)	0.35	25.0%
IGHV unmutated, n (%)	104 (78.8%)	142 (73.0%)	0.29	73.0%
CrCl <60 mL/min, n (%)	35 (26.5%)	62 (32.0%)	0.35	32.0%

Source: Table 2.6.1, p.78 of the submission.

Abbreviations: ACAL, acalabrutinib; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IBR, ibrutinib; IGHV, immunoglobulin heavy chain gene; MAIC, matching adjusted indirect comparison.

[1] Patients in ASCEND who were ECOG PS 2 at baseline (n=19) were not included in the matching because RESONATE did not include patients with this performance status. A further four patients were removed due to missing baseline characteristics therefore 132 ACA patients were matched.

[2] Effective sample size after reweighting.

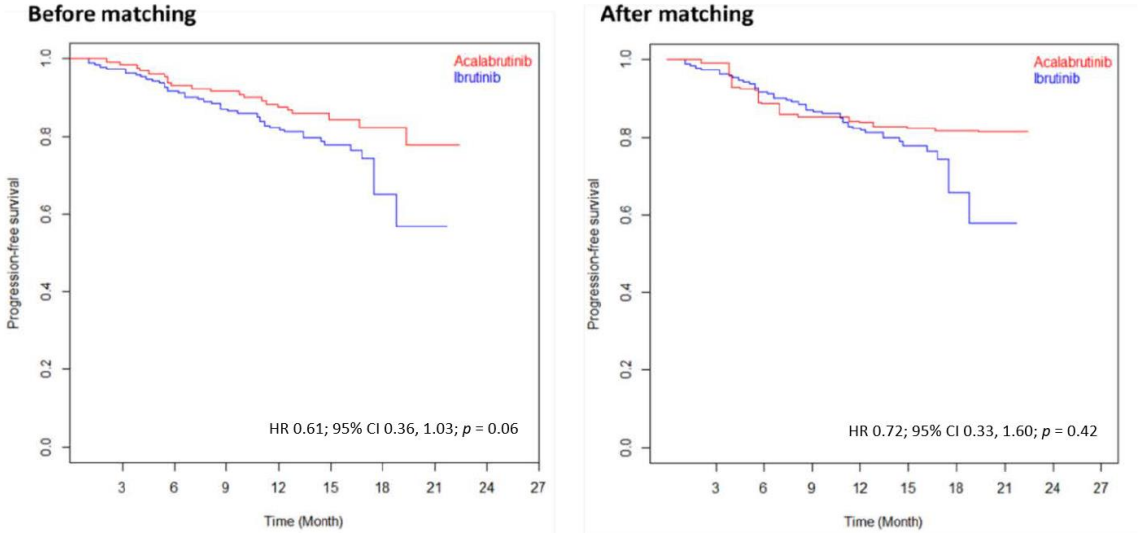
6.30 Matching for the selected variables resulted in a large loss of effective sample size reducing it from 132 patients to 44, suggesting poor overlap between the trial populations. Post-matching patient characteristics for variables that were not matched in the MAIC analysis were not provided in the submission. Due to the interdependence of variables, and different weights applied to each patient, matching of specific characteristics is likely to affect the distribution of other characteristics. The PSCR stated that specific variables were excluded due to high amounts of missing data from RESONATE, variables not collected in ASCEND, and clinical expert opinions. The ESC considered that the resulting effective sample size (N=44) was unlikely to be sufficient to reliably compare treatments and considered that the differing trial populations introduced uncertainty into the MAIC.

6.31 The RESONATE trial required patients to be unsuitable for treatment with a purine analogue based on the presence of at least one of four specified criteria (failure to respond or a progression-free interval of < 3 years from treatment with a purine analogue based therapy and anti-CD20 containing chemo-immunotherapy regimen; age ≥ 70 years; age ≥ 65 years in the presence of co-morbidities; FISH showing 17p deletion in ≥ 20% of cells), whereas the ASCEND trial did not exclude patients on the

basis of purine analogue suitability. The pre-PBAC response stated that the MAIC minimised the impact of the differences in the trial populations by matching patients on variables used to determine fludarabine ineligibility in RESONATE.

6.32 Results for the comparison of investigator-assessed progression-free survival based on a median follow-up of 16.1 months for ASCEND and 19 months for RESONATE (Brown et al., 2018) are presented in Figure 4.

Figure 4: Results for the MAIC of investigator-assessed progression-free survival for acalabrutinib versus ibrutinib



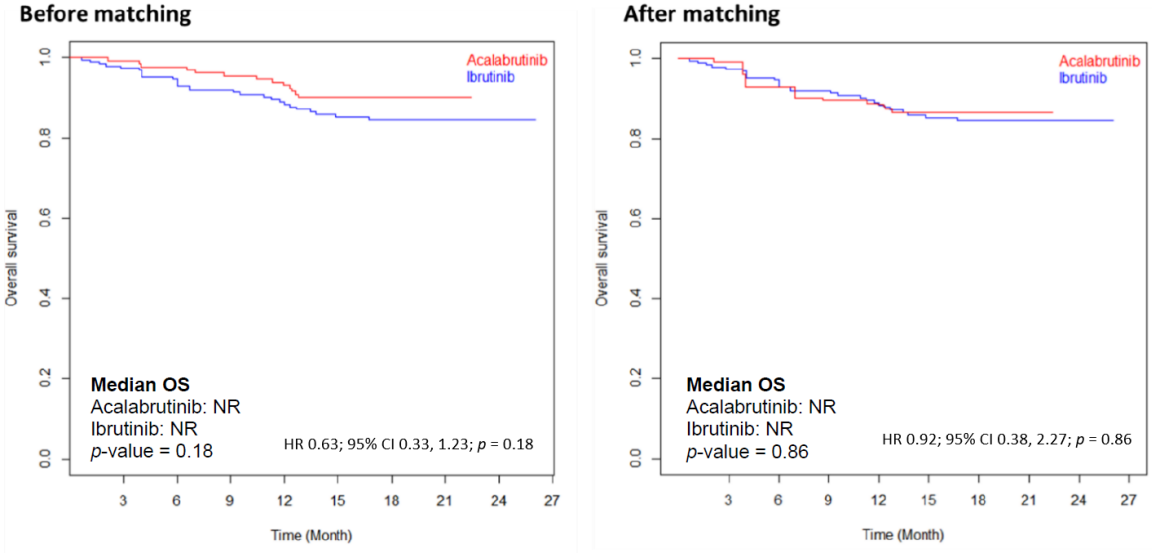
Source: Figure 2.6.1, 80 of the submission.
Abbreviations: CI, confidence interval; HR, hazard ratio.
** Note that the results presented in Figure 4 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for ASCEND and RESONATE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.33 Prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and ibrutinib), the hazard ratio for progression-free survival favoured acalabrutinib but the difference was not statistically significant (HR = 0.61; 95% CI: 0.36, 1.03). After MAIC adjustment, the difference in progression-free survival between acalabrutinib and ibrutinib remained not statistically significant (HR = 0.72; 95% CI: 0.33, 1.60).

6.34 The PBAC noted that the results should be interpreted with caution due to the low effective sample size in the acalabrutinib arm after matching, differences in the duration of follow-up between the trials, and differences between the trials in eligibility criteria (purine analogue suitability) that were not explicitly adjusted for in the MAIC.

6.35 Results for the comparison of overall survival based on a median follow-up of 16.1 months for ASCEND and 19 months for RESONATE (Brown et al., 2018) are presented in Figure 5.

Figure 5: Results for the MAIC of overall survival for acalabrutinib versus ibrutinib



Source: Figure 2.6.2, p.81 of the submission.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.
** Note that the results presented in Figure 5 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for ASCEND and RESONATE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.36 Prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and ibrutinib), the hazard ratio for overall survival favoured acalabrutinib but the difference was not statistically significant (HR 0.63; 95% CI: 0.33, 1.23). After MAIC adjustment, the difference in overall survival between acalabrutinib and ibrutinib remained not statistically significant (HR 0.92; 95% CI: 0.38, 2.27). The PBAC noted that the results should be interpreted with caution due to the low effective sample size in the acalabrutinib arm after matching, the potential impact of patient crossover, and use of post-progression treatments in the included trials.

MAIC of acalabrutinib versus venetoclax plus rituximab

6.37 The number of patients included in the MAIC from the ASCEND trial was 150. The submission stated that this number was lower than the number of patients in the ASCEND trial acalabrutinib arm (N=155) due to incomplete baseline data recording for some patients in some outcomes.

6.38 Table 7 presents the prognostic and treatment effect modifier variables chosen for matching, along with the proportion of patients in the acalabrutinib arm before and after matching.

Table 7: Distribution of effect modifiers and prognostic variables before and after re-weighting for acalabrutinib versus venetoclax plus rituximab

Effect modifier and prognostic characteristics	ACAL unadjusted (N=150)[1]	VEN + RITU (N=195)	*p*-value for difference	ACAL MAIC adjusted (N=86)[2]
Age ≥65, n (%)	94 (62.7%)	97 (50.0%)	<0.05	50.0%
Male, n (%)	105 (70.0%)	136 (71.0%)	0.93	71.0%
17p deletion, n (%)	27 (18.0%)	46 (26.6%)	0.08	26.6%
ECOG score = 0, n (%)	58 (38.7%)	111 (57.2%)	<0.0001	57.2%
ECOG score = 1, n (%)	75 (50.0%)	82 (42.3%)	0.19	42.3%
ECOG score = 2, n (%)	17 (11.3%)	1 (0.5%)	< 0.05	0.5%
Rai stage 3-4, n (%)	61 (40.7%)	45 (23.1%)	<0.0001	23.1%
Prior treatments =1, n (%)	79 (52.7%)	111 (57.2%)	0.47	57.2%
Prior treatments =2, n (%)	38 (25.3%)	57 (29.4%)	0.47	29.4%
Prior treatments ≥3, n (%)	33 (22.0%)	26 (13.4%)	0.68	13.4%
IGHV unmutated, n (%)	117 (78.0%)	133 (68.3%)	0.06	68.3%
TP53 mutation, n (%)	39 (26.0%)	49 (25.0%)	0.93	25.0%

Source: Table 5.6.1, p22 of 'Acalabrutinib_RR CLL_PBAC Appendix 1_supplementary analyses' document.

Abbreviations: ACAL, acalabrutinib; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain gene; MAIC, matching adjusted indirect comparison; RITU, rituximab; VEN, venetoclax.

[1] N=150 rather than 155 due to incomplete baseline data recording for some patients in some outcomes.

[2] Effective sample size after reweighting.

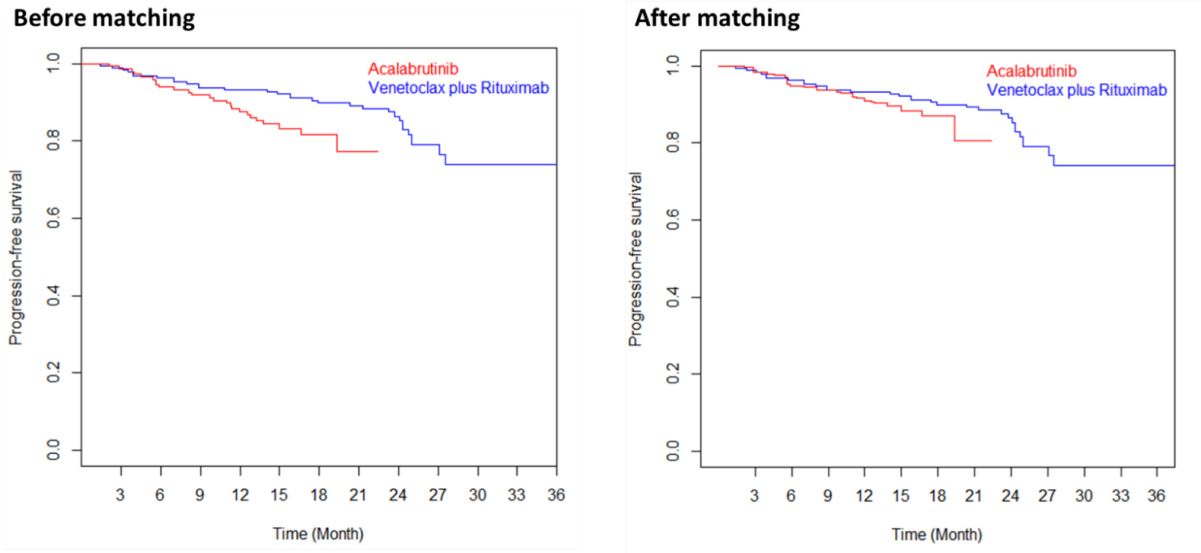
6.39 Matching was constrained by the availability of published baseline characteristics for the MURANO trial, and a number of potential prognostic/effect modifier variables were not matched, including 11q deletion, β_2 microglobulin > 3.5 mg/L, complex karyotype, creatinine clearance < 60 mL/min, and the presence of bulky disease ≥ 5 cm. The reported Rai disease stage for the MURANO trial was Rai stage at diagnosis, whereas for the ASCEND trial it was the Rai stage at baseline/screening, and therefore, the ESC considered that matching of these characteristics was not appropriate.

6.40 Matching for the selected variables resulted in a reduced effective sample size of 86, indicating poor overlap between the included trial populations. Post-matching characteristics for variables not chosen for matching were not provided in the submission. The PSCR added that baseline tumour lysis risk and a proportion of fludarabine refractory patients were excluded due to lack of data for ASCEND.

6.41 The MURANO trial recruited patients with an ECOG of ≤ 1. It may have been more appropriate to exclude the patients with an ECOG of 2 in the ASCEND trial from the analysis, rather than match based on the single patient in the MURANO trial with an ECOG of 2 (who did not meet the trial eligibility criteria).

6.42 Results for the comparison of progression-free survival based on a median follow-up of 16.1 months for ASCEND and 23.8 months for MURANO (Seymour et al., 2018) are presented in Figure 6.

Figure 6: Results for the MAIC of progression-free survival for acalabrutinib versus venetoclax plus rituximab



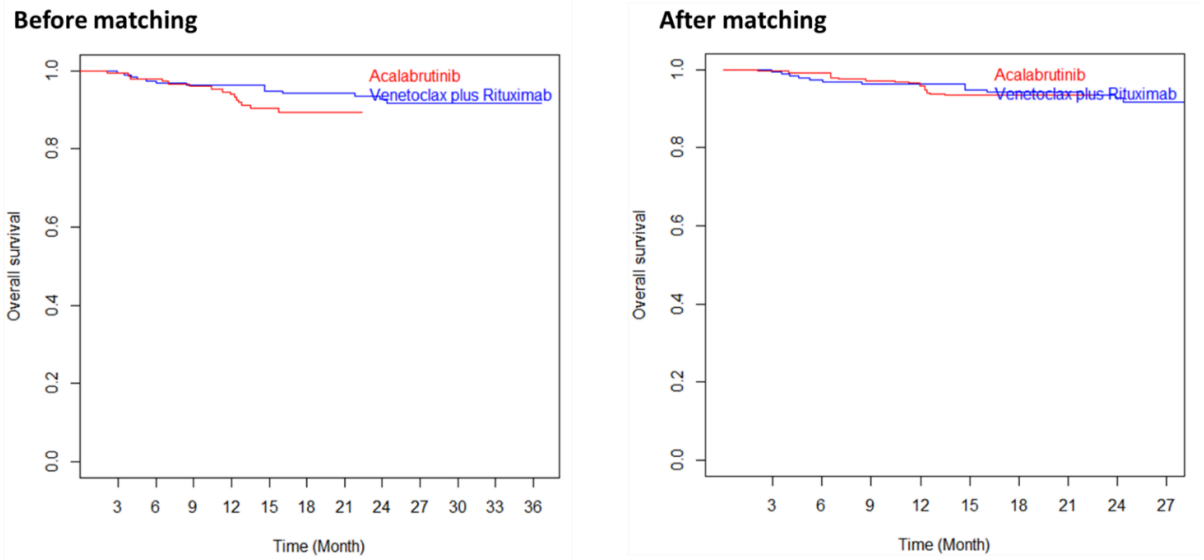
Source: Figure 5.6.1, p.26 of 'Acalabrutinib_RR CLL_PBAC Appendix 1_supplementary analyses' document.

** Note that the results presented in Figure 6 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for ASCEND and MURANO. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.43 Prior to the MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and venetoclax plus rituximab), the hazard ratio for progression-free survival was statistically significant in favour of venetoclax plus rituximab (HR = 2.19; 95% CI: 1.19, 4.03). After MAIC adjustment, the difference in progression-free survival favoured venetoclax plus rituximab but was not statistically significant (HR = 1.62; 95% CI: 0.79, 3.30). The PBAC noted that the results should be interpreted with caution due to the low effective sample size after matching, the inability to match for all prognostic/effect modifier variables, and differences in follow-up durations between the trials.

6.44 Results for the comparison of overall survival based on a median follow-up of 16.1 months for ASCEND and 23.8 months for MURANO (Seymour et al., 2018) are presented in Figure 7.

Figure 7: Results for the MAIC of overall survival for acalabrutinib versus venetoclax plus rituximab



Source: Figure 5.6.2, p.26 of 'Acalabrutinib_RR CLL_PBAC Appendix 1_supplementary analyses' document.
** Note that the results presented in Figure 7 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for ASCEND and MURANO. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.45 Prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and venetoclax plus rituximab), the hazard ratio for overall survival favoured venetoclax plus rituximab but the difference was not statistically significant (HR = 1.91; 95% CI: 0.87, 4.16). After MAIC adjustment, the difference in overall survival between acalabrutinib and venetoclax plus rituximab remained not statistically significant (HR = 1.17; 95% CI: 0.49, 2.82). The PBAC noted that the results should be interpreted with caution due to the low effective sample size in the acalabrutinib arm after matching, the inability to match for all prognostic/effect modifier variables, the potential impact of patient crossover, and the potential impact of post-progression treatments.

Indirect comparisons

6.46 The submission presented the following Bucher method indirect comparisons:

- Acalabrutinib (ASCEND) versus ibrutinib plus bendamustine plus rituximab (HELIOS) using the investigator's choice arm of the ASCEND trial (idelalisib plus rituximab or bendamustine plus rituximab) and the placebo plus bendamustine plus rituximab arm of the HELIOS trial as common reference;
- Acalabrutinib (ASCEND) versus venetoclax plus rituximab (MURANO) using the investigator's choice arm of the ASCEND trial (idelalisib plus rituximab or bendamustine plus rituximab) and the bendamustine plus rituximab arm of the MURANO trial as common reference.

6.47 There were differences in the common reference arms between the trials, suggesting that the Bucher method indirect comparisons may not be appropriate. In the ASCEND trial, patients in the investigator's choice arm received treatment with idelalisib plus

rituximab (77% of patients) or bendamustine plus rituximab (23% of patients). In the HELIOS trial, patients were treated with placebo plus bendamustine plus rituximab. Patients in the MURANO trial received bendamustine plus rituximab. The submission argued that the comparisons were likely to bias against acalabrutinib, as bendamustine plus rituximab is considered inferior to idelalisib plus rituximab.

Indirect comparison of acalabrutinib versus ibrutinib plus bendamustine plus rituximab

6.48 The HELIOS trial compared treatment with ibrutinib plus bendamustine plus rituximab to placebo plus bendamustine plus rituximab. The submission assumed that the ibrutinib plus bendamustine plus rituximab arm of the HELIOS trial could be used as a proxy for the efficacy of ibrutinib monotherapy, based on the results of an analysis by Hillmen et al. (2015). The submission stated that an indirect comparison of safety data from ASCEND and HELIOS was not included due to the additional toxicity expected with the addition of bendamustine and rituximab to ibrutinib. The ESC considered the ibrutinib monotherapy proxy was appropriate for the comparison of efficacy (based on Hillman et al, 2015), but not for safety as the true safety profile of ibrutinib monotherapy could not be determined.

6.49 The submission acknowledged that there were differences between the ASCEND and HELIOS trials that may impact the indirect comparison, including differences in patient characteristics, blinding, follow-up durations, common reference arm treatments, and the number of progression events in each of the common reference arms.

6.50 Table 8 presents the results for the indirect comparison of acalabrutinib versus ibrutinib plus bendamustine plus rituximab for independent review committee-assessed progression-free survival based on the ASCEND (median follow-up 16 months) and HELIOS trials (median follow-up 17 months).

Table 8: Indirect comparison of independent review committee-assessed progression-free survival for acalabrutinib versus ibrutinib plus bendamustine plus rituximab

Trial	Outcome	ACAL	IDEL/BEN + RITU	Absolute difference	HR (95% CI)
ASCEND (16 months)	Progressed, n/N (%)	27/155 (17.4%)	68/155 (43.9%)	26.5%	-
	Median PFS, months (95% CI)	Not reached (NE)	16.5 (14.0, 17.1)	-	**0.31 (0.20, 0.49)**
Trial	**Outcome**	**IBR + BEN + RITU**	**PBO + BEN + RITU**	**Absolute difference**	**HR (95% CI)**
HELIOS (17 months)	Progressed, n/N (%)	56/289 (19.4%)	183/289 (63.3%)	43.9%	-
	Median PFS, months (95% CI)	Not reached (NE)	13.3 (11.3, 13.9)	-	**0.20 (0.15, 0.28)**
Indirect comparison ACAL (16.1 months) vs. IBR + BEN + RITU (17 months)					1.53 (0.89, 2.63)

Source: Table 2.6.10, p.91 of the submission.
Abbreviations: ACAL, acalabrutinib; BEN, bendamustine; CI, confidence interval; HR, hazard ratio; IBR, ibrutinib; IDEL, idelalisib; NE, not estimable; PBO, placebo; RITU, rituximab.
Bolded result indicates statistically significant difference.

6.51 Based on the results of the indirect comparison, treatment with ibrutinib plus bendamustine plus rituximab was associated with a longer duration of progression-free survival compared to acalabrutinib, although the difference was not statistically significant (HR = 1.53; 95% CI: 0.89, 2.63). The PBAC noted that the results should be

interpreted with caution due to differences in trial populations, study design (double-blind versus open label), common reference arms, and event rates.

6.52 Table 9 presents the results of the indirect comparison of acalabrutinib versus ibrutinib plus bendamustine plus rituximab for overall survival based on the ASCEND (median follow-up 16 months) and HELIOS trials (median follow-up 17 months and 34.8 months).

Table 9: Indirect comparison of overall survival for acalabrutinib versus ibrutinib plus bendamustine plus rituximab

Trial	Outcome	ACAL	IDEL/BEN + RITU	Absolute difference	HR (95% CI)
ASCEND (16 months)	Deaths, n/N (%)	15/155 (9.7%)	18/155 (11.6%)	1.9%	-
	Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	-	0.84 (0.42, 1.66)
Trial	**Outcome**	**IBR + BEN + RITU**	**PBO + BEN + RITU**	**Absolute difference**	**HR (95% CI)**
HELIOS (17 months)	Deaths, n/N (%)	NR	NR	NR	-
	Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	-	0.63 (0.39, 1.02)
HELIOS (34.8 months)	Deaths, n/N (%)	NR	NR	NR	**-**
	Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	-	**0.65 (0.45, 0.94)**
Indirect comparison ACAL (16.1 months) vs. IBR + BEN + RITU (17 months)					1.34 (0.58, 3.11)
Indirect comparison ACAL (16.1 months) vs. IBR + BEN + RITU (34.8 months)					1.29 (0.59, 2.80)

Source: Table 2.6.12, p.93 of the submission.
Abbreviations: ACAL, acalabrutinib; BEN, bendamustine; CI, confidence interval; HR, hazard ratio; IBR, ibrutinib; IDEL, idelalisib; NE, not estimable; NR, not reported; PBO, placebo; RITU, rituximab.
Bolded result indicates statistically significant difference.

6.53 Based on the results of the indirect comparison, treatment with ibrutinib plus bendamustine plus rituximab was associated with a longer duration of overall survival compared to acalabrutinib, but the difference was not statistically significant for either the 17-month (HR = 1.34; 95% CI: 0.58, 3.11) or 34.8-month comparisons (HR = 1.29; 0.59, 2.80). The PBAC noted that the results should be interpreted with caution due to differences in trial populations, common reference arms, assessment time points and event rates. Additionally, the reported overall survival results were likely to be affected by patient crossover and the differential use of post-progression treatments.

Indirect comparison of acalabrutinib versus venetoclax plus rituximab

6.54 The submission acknowledged that there were differences between the ASCEND and MURANO trials that may impact the indirect comparison, including differences in patient characteristics, common reference arms, follow-up durations, and the number of progression events in each of the common reference arms.

6.55 Table 10 presents the results of the indirect comparison of acalabrutinib versus venetoclax plus rituximab for independent review committee-assessed progression-free survival based on the ASCEND (median follow-up 16 months) and MURANO trials (median follow-up 23.8 months).

Table 10: Indirect comparison of independent review committee-assessed progression-free survival for acalabrutinib versus venetoclax plus rituximab

Trial	Outcome	ACAL	IDEL/BEN + RITU	Absolute difference	HR (95% CI)
ASCEND (16 months)	Progressed, n/N (%)	27/155 (17.4%)	68/155 (43.9%)	26.5%	-
	Median PFS, months (95% CI)	Not reached (NE)	16.5 (14.0, 17.1)	-	**0.31 (0.20, 0.49)**
Trial	**Outcome**	**VEN + RITU**	**BEN + RITU**	**Absolute difference**	**HR (95% CI)**
MURANO (23.8 months)	Progressed, n/N (%)	NR	NR	NR	-
	Median PFS, months (95% CI)	NR	NR	-	**0.19 (0.13, 0.28)**
Indirect comparison ACAL (16.1 months) vs. VEN + RITU (23.8 months)					1.63 (0.91, 2.94)

Source: Table 5.6.8, p.30 of 'Acalabrutinib_RR CLL_PBAC Appendix 1_supplementary analyses' document.
Abbreviations: ACAL, acalabrutinib; BEN, bendamustine; CI, confidence interval; HR, hazard ratio; IDEL, idelalisib; NE, not estimable; NR, not reported; PFS, progression-free survival; RITU, rituximab; VEN, venetoclax.
Bolded result indicates statistically significant difference.

6.56 Based on the results of the indirect comparison, treatment with venetoclax plus rituximab was associated with a longer duration of progression-free survival compared to acalabrutinib, although the difference was not statistically significant (HR = 1.63; 95% CI: 0.91, 2.94). The PBAC noted that the results should be interpreted with caution due to differences in trial populations, common reference arms, assessment time points, and event rates.

6.57 Table 11 presents the results of the indirect comparison of acalabrutinib versus venetoclax plus rituximab for overall survival based on the ASCEND (median follow-up 16 months) and MURANO trials (median follow-up 23.8 months and 36 months).

Table 11: Indirect comparison of overall survival for acalabrutinib versus venetoclax plus rituximab

Trial	Outcome	ACAL	IDEL/BEN + RITU	Absolute difference	HR (95% CI)
ASCEND (16 months)	Deaths, n/N (%)	15/155 (9.7%)	18/155 (11.6%)	1.9%	-
	Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	-	0.84 (0.42, 1.66)
Trial	**Outcome**	**VEN + RITU**	**BEN + RITU**	**Absolute difference**	**HR (95% CI)**
HELIOS (17 months)	Deaths, n/N (%)	NR	NR	NR	-
	Median OS, months (95% CI)	NR	NR	-	**0.48 (0.25, 0.90)**
HELIOS (34.8 months)	Deaths, n/N (%)	NR	NR	NR	**-**
	Median OS, months (95% CI)	NR	NR	-	**0.50 (0.30, 0.85)**
Indirect comparison ACAL (16.1 months) vs. VEN + RITU (23.8 months)					1.75 (0.68, 4.48)
Indirect comparison ACAL (16.1 months) vs VEN + RITU (34.8 months)					1.68 (0.71, 3.98)

Source: Table 5.6.10, p.32 of 'Acalabrutinib_RR CLL_PBAC Appendix 1_supplementary analyses' document.
Abbreviations: ACAL, acalabrutinib; BEN, bendamustine; CI, confidence interval; HR, hazard ratio; IDEL, idelalisib; NE, not estimable; NR, not reported; OS, overall survival; RITU, rituximab; VEN, venetoclax.
Bolded result indicates statistically significant difference.

6.58 Based on the results of the indirect comparison, treatment with venetoclax plus rituximab was associated with a longer duration of overall survival compared to acalabrutinib, although the difference was not statistically significant for the 23.8-month (HR = 1.75; 95% CI: 0.68, 4.48) or 34.8-month comparisons (HR = 1.68; 95% CI: 0.71, 3.98). The PBAC noted that the results should be interpreted with caution due to differences in the trial populations, common reference arms and follow-up

durations. The reported overall survival results were likely to be affected by patient crossover and the differential use of post-progression treatments.

Comparative harms

6.59 There was limited long-term efficacy and safety data for acalabrutinib. Results presented in the submission were based on an interim analysis of the ASCEND trial, with a median duration of follow-up of 16 months. Table 12 presents the results of safety outcomes for the ASCEND trial at the interim analysis.

Table 12: Summary of safety outcomes for the ASCEND trial at the interim analysis

	ACAL N=155	IDEL + RITU N=118	BEN + RITU N=35
Median duration of follow-up, months (range)	16.1 (0.53–22.41)	15.74 (0.03–22.05)	
Grade 3 or 4 AE, n (%)	70 (45.5%)	101 (65.6%)	15 (42.9%)
Serious AE, n (%)	44 (28.6%)	66 (55.9%)	9 (25.7%)
Treatment related AE, n (%)	101 (65.6%)	111 (94.1%)	24 (68.6%)
Discontinuation due to AE, n (%)	16 (10.4%)	62 (52.5%)	6 (17.1%)
AE leading to death, n (%)	6 (3.9%)	5 (4.2%)	2 (5.7%)
Any AE, n (%)	144 (93.5%)	117 (99.2%)	28 (80.0%)
Any AE incidence >10%, n (%)			
- Headache	34 (22.1%)	7 (5.9%)	0
- Neutropenia	30 (19.5%)	53 (44.9%)	12 (34.3%)
- Diarrhoea	28 (18.2%)	55 (46.6%)	5 (14.3%)
- Anaemia	23 (14.9%)	10 (8.5%)	4 (11.4%)
- Cough	23 (14.9%)	18 (15.3%)	2 (5.7%)
- Upper respiratory tract infection	22 (14.3%)	17 (14.4%)	4 (11.4%)
- Pyrexia	19 (12.3%)	21 (17.8%)	6 (17.1%)
- Thrombocytopenia	17 (11.0%)	16 (13.6%)	5 (14.3%)
- Pneumonia	16 (10.4%)	14 (11.9%)	2 (5.7%)
- Respiratory tract infection	16 (10.4%)	8 (6.8%)	0
- Fatigue	15 (9.7%)	10 (8.5%)	8 (22.9%)
- Nausea	11 (7.1%)	15 (12.7%)	7 (20.0%)
- Rash	10 (6.5%)	16 (13.6%)	2 (5.7%)
- Alanine aminotransferase increased	3 (1.9%)	14 (11.9%)	3 (8.6%)
- Infusion-related reaction	0	9 (7.6%)	8 (22.9%)
Grade ≥3 AE incidence >2%, n (%)	76 (49.4%)	106 (89.8%)	17 (48.6%)
- Neutropenia	24 (15.6%)	47 (39.8%)	11 (31.4%)
- Anaemia	18 (11.7%)	8 (6.8%)	3 (8.6%)
- Pneumonia	8 (5.2%)	10 (8.5%)	1 (2.9%)
- Thrombocytopenia	6 (3.9%)	9 (7.6%)	1 (2.9%)
- Upper respiratory tract infection	3 (1.9%)	4 (3.4%)	1 (2.9%)
- Alanine aminotransferase increased	2 (1.3%)	10 (8.5%)	1 (2.9%)
- Diarrhoea	2 (1.3%)	28 (23.7%)	0
- Neutrophil count decreased	2 (1.3%)	9 (7.6%)	1 (2.9%)
- Aspartate aminotransferase increased	1 (0.6%)	6 (5.1%)	1 (2.9%)
- Febrile neutropenia	1 (0.6%)	3 (2.5%)	1 (2.9%)
- Influenza	1 (0.6%)	2 (1.7%)	1 (2.9%)
- Pyrexia	1 (0.6%)	8 (6.8%)	1 (2.9%)
- Transaminases increased	0	6 (5.1%)	0
- Pneumonia pneumococcal	0	4 (3.4%)	0
- Rash	0	4 (3.4%)	0
- Colitis	0	3 (2.5%)	0
- Granulocytopenia	0	3 (2.5%)	0

Source: Table 2.5.6, p.75 of the submission.
Abbreviations: AE, adverse event; ACAL, acalabrutinib; BEN, bendamustine; IDEL, idelalisib; RITU, rituximab.

6.60 Treatment with acalabrutinib was associated with high rates of treatment-emergent adverse events (93.5%), treatment-related adverse events (65.6%) and Grade 3/4 adverse events (45.5%). There were numerically lower Grade 3/4 adverse events, serious adverse events, treatment-related adverse events, and discontinuations due to adverse events in patients treated with acalabrutinib compared to patients treated

with idelalisib plus rituximab. The ESC considered that these differences were likely to be clinically relevant as idelalisib is notably toxic.

MAIC of acalabrutinib versus ibrutinib

6.61 The submission presented MAICs of acalabrutinib and ibrutinib for Grade 1-4 and Grade 3/4 adverse events based on the results of the ASCEND and RESONATE trials. The MAIC was conducted by matching of patient characteristics that were considered to be prognostic and treatment effect modifier variables for CLL/SLL disease. The ESC considered that these variables may not be relevant to the occurrence of adverse events. The ESC noted that this approach has not been validated and is unlikely to be reliable.

6.62 Adverse event data for ibrutinib were based on various durations of follow-up (9.4 months, 16 months and 19 months), compared to 16.1 months for acalabrutinib. The longer median duration of follow-up for some adverse event outcomes for ibrutinib may bias against ibrutinib, whereas the shorter median duration of follow-up for some adverse event outcomes may bias against acalabrutinib.

6.63 Table 13 presents the results of the MAIC of Grade 3/4 adverse events for acalabrutinib versus ibrutinib.

Table 13: Results of the MAIC of Grade 3/4 adverse events for acalabrutinib versus ibrutinib

Adverse event, any Grade 3/4, %	Unadjusted			MAIC adjusted		
	ACAL (N=132)[1]	IBR (N=195)	RD (95% CI)	ACAL (N=44)[2]	IBR (N=195)	RD (95% CI)
IBR median follow-up: 9.4 months						
Any Grade 3/4	47.0%	51.0%	-4.0 (-15.1, 7.0)	47.4%	51.0%	-3.6 (-23.8, 1.0)
Serious AE	27.3%	42.0%	**-14.7 (-25.0, -4.0)**	29.3%	42.0%	**-12.7 (-23.8, -1.0)**
Infections	13.6%	21.0%	-7.4 (-15.6, 0.0)	11.1%	21.0%	**-9.9 (-18.9, 0.0)**
IBR median follow-up: 16 months						
Anaemia	10.6%	6.0%	4.6 (-1.6, 10.0)	16.5%	6.0%	**10.5 (0.5, 20.0)**
Neutropenia	18.2%	18.0%	0.2 (-8.3, 8.0)	15.7%	18.0%	-2.3 (-11.4, 6.0)
Thrombocytopenia	6.8%	6.0%	0.8 (-4.6, 6.0)	3.4%	6.0%	-2.6 (-6.9, 1.0)
Hypertension	2.3%	6.0%	-3.7 (-7.9, 0.0)	0.4%	6.0%	**-5.6 (-9.0, -2.0)**
Pneumonia	5.3%	9.0%	-3.7 (-9.3, 1.0)	7.7%	9.0%	-1.3 (-9.0, 6.0)
IBR median follow-up: 19 months						
Headache	0.8%	1.5%	-0.7 (-3.0, 1.0)	3.3%	1.5%	1.8 (-3.4, 6.0)
Atrial fibrillation	1.5%	3.6%	-2.1 (-5.4, 10.0)	0.8%	3.6%	-2.8 (-5.7, 0.0)
Diarrhoea	1.5%	4.6%	-3.1 (-6.7, 0.0)	0.3%	4.6%	**-4.3 (-7.3, -1.0)**
Haemorrhage	1.5%	3.0%	-1.5 (-4.7, 1.0)	0.5%	3.0%	-2.5 (-5.0, 0.0)
Fatigue	0.8%	3.6%	-2.8 (-6.0, 0.0)	0.5%	3.6%	**-3.1 (-5.9, 0.0)**
Pyrexia	0.8%	1.5%	-0.7 (-3.0, 1.0)	0.3%	1.5%	-1.2 (-3.0, 0.0)
Nausea	0	1.5%	-1.5 (-3.2, 0.0)	0	1.5%	-1.5 (-3.2, 0.0)
Cough	0	0.5%	-0.5 (-1.5, 0.0)	0	0.5%	-0.5 (-1.5, 0.0)
Peripheral oedema	0	0	0.0 (0.0, 0.0)	0	0	0.0 (0.0, 0.0)
Arthralgia	0	1.5%	-1.5 (-3.2, 0.0)	0	1.5%	-1.5 (-3.2, 0.0)
Constipation	0	0	0.0 (0.0, 0.0)	0	0	0.0 (0.0, 0.0)
Vomiting	0	0	0.0 (0.0, 0.0)	0	0	0.0 (0.0, 0.0)

Source: Table 2.6.4, pp83-84 of the submission.

Abbreviations: ACAL, acalabrutinib; AE, adverse event; IBR, ibrutinib; MAIC, matching adjusted indirect comparison; RD, risk difference.

Bolded results indicate statistically significant difference (p<0.05).

[1] Patients in ASCEND who were ECOG score 2 at baseline (n=19) were not included in the matching because RESONATE did not include patients with this performance status. A further four patients were removed due to missing baseline characteristics therefore 132 ACA patients were matched.

[2] Effective sample size after reweighting.

6.64 Prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and ibrutinib), there was a statistically significant difference favouring acalabrutinib for serious adverse events. After MAIC adjustment, there were statistically significant differences favouring acalabrutinib for serious adverse events and hypertension, and favouring ibrutinib for anaemia. The PBAC noted that the results should be interpreted with caution due to inadequate justification for the application of the MAIC methodology to specific adverse events, the low effective sample size for acalabrutinib, and differences in the duration of follow-up between the trials.

6.65 The proposed restriction includes patients who have developed intolerance to another BTK inhibitor (i.e. ibrutinib) of a severity necessitating permanent treatment withdrawal.

6.66 The submission noted that in a study by Awan et al. (2016), patients with ibrutinib intolerance were successfully treated with acalabrutinib without recurrence of symptoms.

6.67 Another study, Awan et al. (2019), assessed the safety and efficacy of acalabrutinib among an open-label cohort of patients with CLL/SLL who discontinued ibrutinib due to intolerance (as determined by the investigator). The study comprised 33 patients with a median duration of prior ibrutinib treatment of 11.6 months. After a median of 19.0 months treatment (range: 0.2, 30.6), 23 patients remained on acalabrutinib and 10 had discontinued. Grade 3/4 adverse events occurred in 58% of patients, with neutropenia (12%), and thrombocytopenia (9%), the most commonly reported. Of 62 ibrutinib-related adverse events associated with intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib. The study authors noted a number of study limitations, including the use of lower doses and retrospective reporting.

6.68 One additional Phase 2 study of 60 patients was noted during the evaluation (Rogers et al., 2019; NCT02717611). Patients who had discontinued ibrutinib due to Grade 3/4 adverse events or persistent/recurrent Grade 2 adverse events and had progressive disease after ibrutinib discontinuation were treated with acalabrutinib. The median duration of prior ibrutinib therapy was 6 months. At a median follow-up of 19 months (range: 1, 31), 67% of patients remained on acalabrutinib. Discontinuations due to adverse events occurred in 10% of patients.

MAIC of acalabrutinib versus venetoclax plus rituximab

6.69 The submission presented MAICs of acalabrutinib and venetoclax plus rituximab for Grade 1-4 and Grade 3/4 adverse events based on the results of the ASCEND and MURANO trials.

6.70 Table 14 presents the results of the MAIC of Grade 3/4 adverse events for acalabrutinib versus venetoclax plus rituximab.

Table 14: Results of the MAIC of Grade 3/4 adverse events for acalabrutinib versus venetoclax plus rituximab

Adverse event, any Grade 3/4, %	Unadjusted			MAIC adjusted		
	ACAL (N=150)[1]	VEN + RITU (N=194)	RD (95% CI)	ACAL (N=86)[2]	VEN + RITU (N=194)	RD (95% CI)
VEN + RITU median follow-up: 23.8 months						
Any AE	48.7%	82.0%	**-33.3 (-43.0, -23.7)**	40.7%	82.0%	**-41.3 (-51.0, -31.5)**
Serious AE	30.0%	46.4%	**-16.4 (-26.6, -6.2)**	18.9%	46.4%	**-27.5 (-36.6, -18.4)**
Anaemia	11.3%	10.8%	0.5 (-6.2, 7.2)	7.3%	10.8%	-3.5 (-9.9, 3.0)
Neutropenia	19.3%	57.7%	**-38.4 (-47.8, -29.0)**	18.0%	57.7%	**-39.7 (-49.5, -30.0)**
Thrombocytopenia	6.7%	5.7%	1.0 (-4.2, 6.1)	3.8%	5.7%	-1.9 (-6.1, 2.4)
Pneumonia	6.7%	5.2%	1.5 (-3.6, 6.5)	4.7%	5.2%	-0.5 (-5.1, 4.1)
Infections	14.7%	17.5%	-2.8 (-10.6, 5.0)	12.2%	17.5%	-5.3 (-13.1, 2.5)
Infusion reaction	0	1.5%	-1.5 (-3.2, 0.2)	0	1.5%	-1.5 (-3.2, 0.2)
Tumour lysis syndrome	0.7%	3.1%	-2.4 (-5.2, 0.3)	0.6%	3.1%	-2.5 (-5.2, 0.2)

Source: Table 5.6.7, p.29 of 'Acalabrutinib_RR CLL_PBAC Appendix 1_supplementary analyses' document.
Abbreviations: ACAL, acalabrutinib; CI, confidence interval; IBR, ibrutinib; MAIC, matching adjusted indirect comparison; RD, risk difference.
[1] N=150 rather than 155 due to incomplete baseline data recording for some patients in some outcomes.
[2] Effective sample size after reweighting.

6.71 Prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and venetoclax plus rituximab), there was a statistically significant difference favouring

acalabrutinib for any Grade 3/4 adverse event, serious adverse events and neutropenia. These events remained statistically significantly different after MAIC adjustment. The PBAC noted that the results should be interpreted with caution due to inadequate justification for the application of the MAIC methodology to specific adverse events, the relatively low effective sample size for acalabrutinib, and differences in the duration of follow-up between the trials.

Benefits/harms

6.72 Noting that the results of the MAIC of acalabrutinib and ibrutinib presented in the submission were highly uncertain, the PBAC considered it likely that patients treated with acalabrutinib would experience a similar duration of progression-free survival and overall survival compared to ibrutinib, and that, although overall safety would likely be non-inferior, for every 100 patients treated with acalabrutinib compared to ibrutinib it was estimated that:

- approximately 11 more patients would experience Grade 3/4 anaemia;
- approximately 6 fewer patients would experience Grade 3/4 hypertension;
- approximately 4 fewer patients would experience Grade 3/4 diarrhoea;
- approximately 3 fewer patients would experience Grade 3/4 fatigue
- approximately 3 fewer patients would experience Grade 3/4 atrial fibrillation; and
- approximately 3 fewer patients would experience Grade 3/4 haemorrhage.

6.73 The ESC noted that acalabrutinib resulted in a potentially reduced risk of atrial fibrillation and haemorrhage compared to ibrutinib (as shown in Table 13) and considered that these reductions were likely to be clinically relevant for some patients. The PBAC considered the data remained uncertain, although noted that a reduced risk of atrial fibrillation and haemorrhage compared with ibrutinib may provide a suitable alternative treatment for some patients, particularly those who are older and who have significant comorbidities.

Clinical claim

6.74 The submission described acalabrutinib as non-inferior in terms of effectiveness, and superior in terms of safety compared to ibrutinib.

6.75 In terms of the efficacy claim:

- The results of the unanchored MAIC of acalabrutinib versus ibrutinib were highly uncertain. Matching of the selected prognostic and treatment effect modifier variables resulted in an effective sample size of 44 (from 132), suggesting poor overlap between the trial populations. Additionally, it was unclear whether all relevant prognostic and treatment effect modifier variables were identified and matched in the analysis. The ESC considered that the effective sample size may not be sufficient to measure a clinically meaningful difference; however, it is likely that acalabrutinib is of a similar efficacy to ibrutinib in this population. The pre-PBAC response stated that the MAIC minimised the impact of the differences in trial

population and that there is a role for population adjusted indirect comparison methods to facilitate health technology assessment.

- The Bucher method indirect comparison was unreliable given differences between the ASCEND and HELIOS trials, including differences in trial populations, study design and common reference arms. Additionally, the comparison relied on the use of ibrutinib plus bendamustine plus rituximab as a proxy for ibrutinib monotherapy. The ESC considered that the use of the ibrutinib proxy for ibrutinib monotherapy proxy was only appropriate for the comparison of efficacy, but not safety.
- No non-inferiority margins for progression-free survival or overall survival were proposed in the submission. The lack of a statistically significant difference for progression-free survival or overall survival may not be sufficient to establish non-inferiority, as the 95% confidence intervals were wide and may include a clinically important difference. The PSCR noted that there are no widely accepted non-inferiority margins in this disease area, in addition the PBAC submission for venetoclax plus rituximab in November 2018, did not nominate a non-inferiority margin. The ESC noted the previous recommendation, but considered the lack of a statistically significant difference may not be sufficient to establish non-inferiority.

6.76 The ESC considered that acalabrutinib was likely to be non-inferior compared to ibrutinib in terms of efficacy. Overall, the PBAC considered that the claim of non-inferior comparative effectiveness was likely to be reasonable, although it noted that the results of the unanchored MAICs and indirect comparisons of acalabrutinib versus ibrutinib were highly uncertain.

6.77 In terms of safety:

- The results of the MAIC of safety outcomes were considered to be unreliable, as the submission did not adequately justify the application of the MAIC methodology (based on adjustment for CLL/SLL disease prognostic and treatment effect modifier variables) to specific adverse event outcomes. The PSCR argued that the application of the MAIC to adverse events was performed to support the results of the naïve comparisons which suggest a superior safety profile for acalabrutinib. The PSCR acknowledged the application of the MAIC methodology was limited; however, it maintained that acalabrutinib is superior in safety to ibrutinib because it is more selective based on the results of in vivo/in vitro studies presented in the submission.

6.78 The ESC considered that the safety data was unreliable and that it remains unclear whether the results of the in vivo/in vitro studies will translate into clinically meaningful differences in safety. The PBAC considered that the claim of superior comparative safety of acalabrutinib to ibrutinib was not adequately supported by the data due to the results of the MAIC of safety outcomes which were considered to be unreliable. Although the PBAC considered that acalabrutinib was likely to present a

different toxicity profile to ibrutinib for some patients, overall, it considered that acalabrutinib was likely to be non-inferior to ibrutinib in terms of comparative safety.

6.79 The submission also presented the results of a comparison of acalabrutinib and venetoclax plus rituximab. While a clinical claim was not explicitly included, the submission stated that there was no statistically significant differences between them based on the comparisons of progression-free survival and overall survival presented in the submission. However, the following issues were noted:

- The results of the unanchored MAIC of acalabrutinib versus ibrutinib were highly uncertain. Matching for the selected variables resulted in an effective sample size of 86 (from 150), indicating relatively poor overlap between the included trial populations. Matching was constrained by the availability of baseline characteristics for the MURANO trial, and a number of potential prognostic/effect modifier variables were not included in the analysis.
- The submission did not adequately justify the application of the MAIC methodology (based on adjustment for CLL/SLL disease prognostic and treatment effect modifier variables) to specific adverse event outcomes.
- Comparison of adverse events was affected by large differences in follow-up durations between the trials, which biased against venetoclax plus rituximab.
- The Bucher method indirect comparison may not be reliable due to differences between the ASCEND and MURANO trials, including differences in trial populations, common reference arms and assessment time points.

6.80 The PBAC agreed with ESC and considered that the comparisons resulted in a high level of uncertainty.

Economic analysis

6.81 The submission presented a cost-minimisation analysis of acalabrutinib versus ibrutinib based on the claim of non-inferior effectiveness and superior safety.

6.82 The equi-effective doses were based on the doses of acalabrutinib and ibrutinib used in the ASCEND and RESONATE trials. These doses were consistent with the doses recommended in the respective Product Information documents. For both acalabrutinib and ibrutinib, treatment is recommended to continue until disease progression or unacceptable toxicity.

6.83 The submission proposed the following equi-effective doses:

> Acalabrutinib 100 mg twice daily for a median duration of [redacted] months = Ibrutinib 420 mg once daily for a median duration of [redacted] months.

6.84 The reported median treatment durations presented in the proposed equi-effective doses may not be reasonable, given that the values reported for acalabrutinib in the clinical study report and for ibrutinib in Brown et al. (2014), did not represent the actual median treatment durations, which had not yet been reached (80.6% of acalabrutinib patients and 76% of ibrutinib patients remained on treatment at the respective assessment time-points). Additionally, the reported median treatment durations may have been affected by other factors, such as differences in the study populations, trial design, and the duration of follow-up between the trials. The PSCR reiterated that the cost-minimisation analysis was based on the most accurate data available. The ESC considered that it was likely that the treatment durations were underestimated.

6.85 The ESC considered that it may have been more appropriate to compare mean treatment durations and mean dose intensity, instead of using median treatment duration. However, noting that the mean treatment duration and dose intensity for ibrutinib were not reported in Brown et al. (2014), the ESC recalled that when considering venetoclax plus rituximab in the relapsed or refractory setting that the PBAC recommended that the cost-minimisation analysis should be based on the duration of ibrutinib which was accepted at the time of its initial PBS listing and include the dose intensity of each medicine (paragraph 7.8, Venetoclax Public Summary Document (PSD), November 2018). The ESC considered that the same approach should be adopted for the cost minimisation analysis between acalabrutinib and ibrutinib.

6.86 The PBAC agreed with ESC in that the same approach taken for the venetoclax submission in November 2018 should be adopted, and that the duration of treatment for acalabrutinib should equal that which was accepted for ibrutinib at the time of its PBS listing.

6.87 The cost-minimisation analysis included costs associated with Grade 1/2 diarrhoea and vomiting, and Grade 3/4 hypertension, infection, anaemia and diarrhoea. The rates of adverse events for acalabrutinib and ibrutinib were based on the adverse event rates reported in the MAIC analysis, which were not considered reliable.

6.88 Based on the included adverse event costs and proportions, the estimated cost of treating adverse events was $645.72 for acalabrutinib and $1,581.67 for ibrutinib, a difference of $935.96. Given the lack of available head-to-head safety data, and the uncertainty associated with the MAIC analysis of safety outcomes, the evaluators considered it may be more appropriate to exclude adverse event costs from the cost-minimisation analysis. The PSCR stated that the data presented was reasonable to support the differences in the safety profile between acalabrutinib and ibrutinib, and that the cost-minimisation analysis excluded the majority of costs associated with Grade 1/2 adverse events, which was considered conservative. The ESC, noting the high degree of uncertainty with the safety comparison, considered that the cost minimisation analysis should only include cost offsets related to atrial fibrillation and haemorrhage. The pre-PBAC response presented the results of an adjusted cost-

minimised analysis only including Grade 3/4 atrial fibrillation (acalabrutinib arm: $24; ibrutinib arm: $107) and haemorrhage (acalabrutinib arm: $25; ibrutinib arm: $151) costs.

6.89 However, the PBAC considered that overall the superior comparative safety claim was inadequately supported and acalabrutinib was likely to be non-inferior to ibrutinib. The PBAC therefore agreed with the evaluator option and recommended that adverse event costs were excluded from the cost-minimisation analysis.

6.90 The PBAC noted the reduced risk of atrial fibrillation and haemorrhage compared to ibrutinib for some patients. The PBAC considered that if these cost offsets were to be included in the cost-minimisation analysis, use of acalabrutinib would need to be restricted to the patient population who are intolerant to ibrutinib.

Acalabrutinib cost/patient/year

6.91 Table 15 presents the drug cost per patient per year for acalabrutinib and ibrutinib, based on published prices and the submission's proposed duration of therapy. The PBAC, noting that it did not accept the different treatment durations or adverse event differences between acalabrutinib and ibrutinib, considered that the effective cost per patient per year of acalabrutinib would be equal to that of ibrutinib.

Table 15: Drug cost per patient for acalabrutinib and ibrutinib as presented in the submission (published prices)

	ACAL			IBR		
	Trial dose and duration	**Economic analysis**	**Financial estimates**	**Trial dose and duration**	**Economic analysis**	**Financial estimates**
Dose	200 mg/day	200 mg/day	200 mg/day	420 mg/day	420 mg/day	420 mg/day
Median duration	[redacted] months	[redacted] months	NE[1]	[redacted] months	[redacted] months	NE[1]
Mean dose intensity	97.32%	100%	100%	NR	100%	100%
Cost/patient/course[2]	$[redacted][3]	$[redacted][3]	NE[1]	NE	$[redacted]	NE[1]
Cost/patient/year	$[redacted][3]	$[redacted][3]	$[redacted][3]	NE	$[redacted]	$[redacted]

Source: Table 32, pp142-143 of the submission.
Abbreviations: ACAL, acalabrutinib; IBR, ibrutinib; NE, not estimable; NR, not reported.
[1] Financial estimates were derived from projected ibrutinib scripts. The underlying treatment duration for ibrutinib was not estimated.
[2] Treatment course based on the reported median treatment duration.
[3] Based on the cost-minimised DPMQ for acalabrutinib of $[redacted]. The requested published price of $[redacted] was higher than the price derived in the cost-minimisation based on the ibrutinib published price.

Estimated PBS usage & financial implications

6.92 This submission was not considered by DUSC. The submission used a market-share approach to estimate the utilisation and financial impacts associated with the PBS listing of acalabrutinib. The sources of data used in the financial estimates are presented in the table below.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Current utilisation of therapies among patients with relapsed/refractory CLL/SLL	12,640 scripts. PBS statistics script data for ibrutinib, venetoclax and idelalisib from September 2018 and August 2019.	Chemo-immunotherapy combinations (such as chlorambucil plus rituximab) were not included in the analysis which may have resulted in an underestimation of the total relapsed/refractory CLL/SLL market.
Annual growth in relapsed/refractory CLL/SLL scripts	5.21% per year. Derived based on the mean annual growth in the 5-year CLL prevalence rate from 2009 (4,146) to 2012 (4,828) reported in the AIHW 'Cancer in Australia 2014' report.	May underestimate growth if patients are likely to cycle through available therapies. PBAC noted that the estimated market for R/R CLL/SLL has previously been accepted in the ibrutinib and venetoclax RSA, and no additional cycling of treatments is an option with acalabrutinib (i.e. patents intolerant or unsuitable for ibrutinib will be treated with acalabrutinib – these are not additional patients).
CLL/SLL scripts per year	10,000 to < 20,000 in Year 1 increasing to 20,000 to < 30,000 in Year 6. Estimated current utilisation of 12,640 scripts per month extrapolated to Year 1 of listing based on assumed annual growth in relapsed/refractory CLL/SLL scripts of 5.21%.	There may be potential for acalabrutinib to substitute for other therapies (including venetoclax plus rituximab, idelalisib plus rituximab, chemo-immunotherapy combinations) among patients with prior ibrutinib intolerance, or among patients considered unsuitable for ibrutinib due to comorbidities.
Market share (ACAL not listed)	IBR: 90%; VEN + RITU: 10%; IDEL + RITU: 0%. Assumption based on expert opinion.	Chemo-immunotherapy combinations (such as chlorambucil plus rituximab) were excluded from the analysis. VEN + RITU was only recently listed for this indication and may achieve a higher market share than assumed given the fixed duration of treatment.
Proportion of IBR displaced by ACAL (ACAL listed)	35% in Year 1 increasing to 60% in Year 6. Assumption based on expert opinion.	The ESC considered that the estimated proportion of displacement was overestimated as it was: - unclear whether clinicians would initiate relapsed/refractory patients on acalabrutinib based on the claimed safety advantages or with ibrutinib given the longer duration of clinical trial data; - unclear whether patients currently treated with ibrutinib would switch to acalabrutinib based on the claimed safety advantages.
Adjustment factor	1.05. The number of acalabrutinib scripts was estimated by applying an adjustment factor to the estimated number of displaced ibrutinib scripts. The adjustment factor was based on differences in pack sizes and differences in the assumed median treatment durations for ibrutinib and acalabrutinib (ibrutinib: 16.0 months; acalabrutinib: 15.7 months).	The submission did not adequately justify the assumption of different treatment durations for ibrutinib and acalabrutinib. The median treatment durations reported for acalabrutinib in the clinical study report and for ibrutinib in Brown et al. (2014) did not represent the underlying median treatment durations, which had not yet been reached.
ACAL DPMQ	$[redacted]. DPMQ based on cost-minimisation of acalabrutinib to ibrutinib.	The requested published price of $[redacted] was higher than the price derived in the cost-minimisation based on the ibrutinib published price.

Source: Table 4.1.1, p.109; Table 4.2.2, p.111; Table 4.2.3, p.112; Table 4.2.6, p.113; Table 4.2.7, p.113; Table 4.2.8, pp113-114; Table 4.2.10, p.115 of the submission; 'Section 4 _Acalabrutinib BIM model_FINAL' Excel workbook.

Abbreviations: ACAL, acalabrutinib; CLL, chronic lymphocytic anaemia; DPMQ, dispensed price for maximum quantity; IBR, ibrutinib; IDEL, idelalisib; RITU, rituximab; VEN, venetoclax.

6.93 Table 17 presents the estimated financial implications for the health budget of listing acalabrutinib, based on the cost-minimised price of acalabrutinib (DPMQ $[redacted]) and the published price of ibrutinib (DPMQ $8,785.41).

Table 17: Estimated extent of use and financial impact of acalabrutinib

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Cost of listing ACAL						
Estimated scripts for IBR, VEN, IDEL (relapsed/refractory CLL/SLL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ibrutinib scripts without ACAL listing (90% of market)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of ibrutinib scripts displaced by ACAL	35%	45%	55%	60%	60%	60%
Displaced ibrutinib scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjustment factor[1]	1.05	1.05	1.05	1.05	1.05	1.05
Total ACAL scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS/RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayments ($14.43 per script)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net PBS/RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in cost of IBR with ACAL listing						
Displaced ibrutinib scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS/RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayments ($14.43 per script)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net PBS/RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/RPBS						
Cost of ACAL	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of displaced IBR	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall net cost of ACAL	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table 4.2.8, p.113; Table 4.2.11, p.115; Table 4.2.13, p.116; Table 4.3.4, p.118; Table 4.4.1, p.120 of the submission.
Abbreviations: ACAL, acalabrutinib; IBR, ibrutinib; IDEL, idelalisib.
[1] Adjustment factor applied to adjust for differences in pack sizes and differences in the assumed median treatment durations for ibrutinib and acalabrutinib (16.0 months for ibrutinib and 15.7 months for acalabrutinib).

The redacted table shows that at Year 6, the estimated number of acalabrutinib scripts was 10,000 to < 20,000.

6.94 The submission estimated a net cost to the PBS of $0 to < $10 million in Year 1 of listing, increasing to $0 to < $10 million in Year 6, an estimated net cost of $0 to < $10 million over the first six years of listing. The net cost was driven by the higher price of acalabrutinib compared to ibrutinib, which was partially offset by the shorter assumed treatment duration for acalabrutinib (15.7 months versus 16.0 months for ibrutinib) and a small increase in copayments for acalabrutinib compared to ibrutinib due to differences in pack sizes. The PBAC noted that acalabrutinib would essentially be cost-neutral to ibrutinib if the cost-minimisation analysis was recalculated to include the

same duration of treatment for acalabrutinib and ibrutinib and exclude adverse event costs.

6.95 The ESC noted that the utilisation/financial estimates were uncertain due to the following issues:

- The submission did not adequately justify the assumed difference in treatment durations for ibrutinib and acalabrutinib.
- Ibrutinib received a positive recommendation at the November 2019 meeting for the first-line treatment of CLL/SLL patients with 17p deletion (PBAC Outcomes, November 2019 PBAC meeting). Use of ibrutinib in the first-line setting is likely to result in a reduction in use of BTK inhibitors in the second-line setting.
- The submission noted that patients with prior intolerance to ibrutinib (requiring treatment withdrawal) and patients considered unsuitable for ibrutinib due to the risk of adverse events, may also be treated with acalabrutinib. In this case, acalabrutinib utilisation may increase due to substitution for other therapies, including venetoclax plus rituximab, idelalisib plus rituximab, and chemo-immunotherapy regimens.
- The assumed ibrutinib displacement rates were considered highly uncertain and overestimated as it was unclear whether patients currently treated with ibrutinib would switch to acalabrutinib based on the claimed safety advantages. The ESC considered that clinicians would be likely continue to recommend ibrutinib unless there was a clear contraindication or interaction with ibrutinib. The ESC considered that ibrutinib displacement would more likely be in the range of 10% to 30%. The pre-PBAC response noted that estimates in the use of acalabrutinib in R/R CLL treatment setting will most likely reach a steady state market share of approximately 50% (based on interim market research data). The pre-PBAC response considered that over time, newer patients will be initiated on acalabrutinib over ibrutinib due to its more favourable safety profile. The PBAC considered that the estimated rate of uptake remained highly uncertain.
- Treatment with venetoclax plus rituximab is based on a fixed treatment duration which may be preferred by patients/clinicians, therefore the assumed market share of 10% may be an underestimate. The pre-PBAC response added that the assumed market share of 10% was based on current PBS utilisation data, and agreed that it may be an underestimate since venetoclax plus rituximab was only PBS-listed on 1 March 2019.
- There may be a small potential for use of acalabrutinib in combination with other agents, such as CD20 antagonists (i.e. outside of the proposed restriction), or in the first-line setting.

6.96 The submission estimated that there would be approximately < 500 grandfathered patients at the time of listing. The submission inappropriately did not include these patients in the budget impact estimates.

6.97 The submission noted that R/R CLL/SLL patients currently undergo testing for 17p deletion via FISH (MBS item 73343) to assess eligibility for treatment with ibrutinib, and argued that no net change in utilisation/cost of MBS item 73343 is expected with acalabrutinib listing.

Financial Management – Risk Sharing Arrangements

6.98 No risk sharing arrangements (RSA) are proposed in the submission.

6.99 The PBAC considered that it would be appropriate for acalabrutinib to join the current RSA for RR CLL/SLL.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of acalabrutinib, for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL)/small lymphocytic leukaemia (SLL) considered unsuitable for treatment or retreatment with a purine analogue. The PBAC recommended listing on a cost-minimisation basis to ibrutinib, with equivalent treatment duration; however, it did not accept the proposed adverse event cost offsets. The PBAC recommended acalabrutinib be included in the existing risk sharing agreement (RSA) for R/R CLL/SLL, with no change to the annual expenditure caps.

7.2 The PBAC noted that the requested restriction was based on the current listing for ibrutinib in R/R CLL/SLL and the inclusion criteria in the key acalabrutinib trial. The PBAC considered that the acalabrutinib listing should align with the current PBS listing for ibrutinib in terms of:

- the authority level, i.e. Authority Required (Telephone) for both initial and continuing restrictions;
- the WHO performance status. The proposed restriction, like the key acalabrutinib trial, requested patients have a WHO status of ≤ 2 at initiation (less than 14% of patients in the ASCEND trial had a WHO performance status of 2); however, the current ibrutinib restriction requires a WHO status of ≤ 1; and
- include a grandfathering restriction.

7.3 The PBAC noted that acalabrutinib was a more selective inhibitor of Bruton's tyrosine kinase (BTK) than ibrutinib and this may mean a lower incidence of some adverse events (e.g. haemorrhage and atrial fibrillation) for some patients. Thus, the PBAC accepted the additional clinical criteria in the proposed restriction that allowed patients to have received a prior BTK inhibitor if they have developed intolerance of a severity necessitating permanent treatment withdrawal in the R/R CLL/SLL setting. The PBAC noted flow-on restriction changes would be required for ibrutinib in the R/R CLL/SLL setting.

7.4 The PBAC noted that advice from the Medical Services Advisory Committee (MSAC) was still pending to include acalabrutinib on the existing MBS Item 73343 for the purpose of assessing PBS eligibility for acalabrutinib treatment.

7.5 The PBAC considered that ibrutinib was the appropriate comparator. The PBAC agreed with the submission claim that acalabrutinib would provide an alternative treatment option for patients who are intolerant to ibrutinib and for patients considered unsuitable for ibrutinib due to safety concerns. However, it noted that the submission was not seeking listing for this population exclusively, but for the whole R/R CLL/SLL population. The PBAC also accepted venetoclax plus rituximab as an appropriate supplementary comparator. However, venetoclax would likely be displaced, rather than replaced, by acalabrutinib. The PBAC did not consider idelalisib plus rituximab to be an appropriate comparator due to its higher toxicity and lower efficacy.

7.6 The PBAC noted that no head-to-head trials comparing acalabrutinib with ibrutinib (or with venetoclax plus rituximab) were available. The submission presented unanchored matching adjusted indirect comparisons (MAICs) and Bucher method indirect comparisons between acalabrutinib and ibrutinib (and venetoclax plus rituximab) for efficacy and safety.

7.7 The results from the MAIC demonstrated that acalabrutinib and ibrutinib were not statistically different in terms of progression free survival (HR = 0.72; 95% CI: 0.33, 1.60) or overall survival (HR = 0.92; 95% CI: 0.38, 2.27). The PBAC considered that the results of the MAICs were uncertain due to the low effective sample size in the acalabrutinib arm after matching (N=44, reduced from 132), differences in the duration of follow-up between the trials and differences between the trials in eligibility criteria.

7.8 The results of the indirect comparison between acalabrutinib and ibrutinib using the Bucher method demonstrated no statistically significant differences in terms of progression free survival (HR = 1.53; 95% CI: 0.89, 2.63) and overall survival (HR = 1.34; 95% CI: 0.58, 3.11). The PBAC considered that the results of the indirect comparisons were uncertain due to differences in the trial populations, study design, common reference arms and event rates.

7.9 Overall, the PBAC accepted the evidence, while uncertain, supported a claim of non-inferior comparative effectiveness compared to ibrutinib.

7.10 The PBAC considered the safety of acalabrutinib to be difficult to determine due to inadequate justification for the application of the MAIC methodology to specific adverse events, the low effective sample size for acalabrutinib, and differences in the duration of follow-up between the trials. However, overall, the PBAC considered that the safety of acalabrutinib is likely to be non-inferior to ibrutinib, and that acalabrutinib appears likely to be safe to use after treatment with ibrutinib, which is important for the population of patients that would benefit from acalabrutinib after ceasing ibrutinib due to intolerability.

7.11 The PBAC noted that the submission presented a cost-minimisation analysis between acalabrutinib and ibrutinib and considered that this was appropriate. The PBAC considered that the cost-minimisation analysis should:

- adopt the same approach taken for the November 2018 venetoclax cost-minimisation with ibrutinib. The duration of treatment for acalabrutinib should equal that which was accepted for ibrutinib at the time of its PBS listing; and
- not include adverse events costs due to the unreliability of the data presented in the MAIC
- The PBAC considered that the equi-effective doses were:

  Acalabrutinib 100 mg twice daily = Ibrutinib 420 mg once daily

7.12 In terms of the estimated financial impact, the PBAC considered that acalabrutinib would essentially be cost-neutral to ibrutinib. The PBAC considered that the estimated rate of uptake was highly uncertain.

7.13 The PBAC noted that a two tier RSA is in place for R/R CLL/SLL that encompasses both ibrutinib and venetoclax. The PBAC recommended that acalabrutinib join the current arrangement and considered that no changes to the subsidisation caps would be appropriate.

7.14 The PBAC recommended that a grandfather listing be in operation for 12 months to transition the approximately < 500 patients who commenced on non-PBS subsidised acalabrutinib through a compassionate access program.

7.15 The PBAC recommended that under Section 101(3BA) of the *National Health Act, 1953* that acalabrutinib should be treated as interchangeable on an individual patient basis with ibrutinib.

7.16 The PBAC advised that acalabrutinib is not suitable for prescribing by nurse practitioners.

7.17 The PBAC recommended that the Early Supply Rule should apply to be consistent with the listing for ibrutinib.

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

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
ACALABRUTINIB acalabrutinib 100 mg capsule, 56	NEW	1	56	5	Calquence®	AstraZeneca Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒Authority Required – Telephone/Electronic/Emergency
Indication: Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) **Treatment Phase:** Initial treatment **Clinical criteria:** ▪ The treatment must be the sole PBS-subsidised therapy for this condition **AND** ▪ The condition must have relapsed or be refractory to at least one prior therapy **AND** ▪ Patient must have a WHO performance status of 0 or 1 **AND** ▪ Patient must not have previously received PBS-subsidised treatment with this drug for this condition **AND** ▪ Patient must be considered unsuitable for treatment or retreatment with a purine analogue **AND** ▪ Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease); 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 CLL/SLL
Prescribing Instructions: A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following: a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles; b) Age is 70 years or older; c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen; d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia; e) Evidence of one or more 17p chromosomal deletions demonstrated by a test method listed in the Medical Benefits Schedule for such a purpose
Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒Authority Required – Telephone/Electronic/Emergency
Indication: Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) **Treatment Phase:** Continuing treatment of relapsed or refractory CLL/SLL **Clinical criteria:** ▪ The treatment must be the sole PBS-subsidised therapy for this condition **AND** ▪ Patient must have previously received PBS-subsidised treatment with this drug for this condition

AND

- Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

Administrative Advice:
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.

Category / Program: GENERAL – General Schedule (Code GE)

Prescriber type: ☐Dental ☒ Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Restriction Level / Method: ☒ Authority Required – Telephone/Electronic/Emergency

Indication: Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)

Treatment Phase: Grandfather treatment (initial treatment in a patient commenced on non-PBS subsidised treatment)

Clinical criteria:

- Patient must have previously received non-PBS-subsidised treatment with this drug for relapsed or refractory CLL/SLL prior to 1 Month 202X

  AND
- The treatment must be the sole PBS-subsidised therapy for this condition

  AND
- 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
- Patient must have had a WHO performance status of 0 or 1 prior to initiating non-PBS subsidised treatment with this drug for this condition

  AND
- Patient must have been considered unsuitable for treatment or retreatment with a purine analogue prior to initiating non-PBS subsidised treatment with this drug for this condition

  AND
- Patient must be considered unsuitable for treatment or retreatment with a purine analogue

  AND
- Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease) prior to initiating non-PBS subsidised treatment with this drug for this condition; 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 CLL/SLL prior to initiating non-PBS subsidised treatment with this drug for this condition

  AND
- Patient must not have developed disease progression while receiving treatment with this drug for this condition

Prescribing Instructions:
A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:
a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles;
b) Age is 70 years or older;
c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;
d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;
e) Evidence of one or more 17p chromosomal deletions demonstrated by a test method listed in the Medical Benefits Schedule for such a purpose

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.
This grandfathering restriction will cease to operate from 12 months after the specified date in the clinical criteria
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.

8.2 Flow-on changes to the existing Relapsed or refractory CLL/SLL ibrutinib initial treatment listing - add a new clinical criterion to ensure patients have not previously received PBS-subsidised treatment with another BTK inhibitor (unless intolerant) as follows:

Clinical criteria:
Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease); 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 CLL/SLL

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.