An addendum to this Public Summary Document has been included at the end of the document.

6.01 ACALABRUTINIB, Tablet, 100 mg, Calquence®, ASTRAZENECA PTY LTD.

Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (telephone/online) listing for acalabrutinib for use in combination with venetoclax (AV) in a fixed duration (FD) regimen for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

1.2 Listing was requested on the basis of a cost-minimisation approach versus the FD regimens of ibrutinib in combination with venetoclax (IV) and venetoclax in combination with obinutuzumab (VO).

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

Component	Description
Population	Patients with previously untreated CLL or SLL
Intervention*	AV: Acalabrutinib (Cycles 1 to 14): 100 mg orally twice daily Venetoclax (Cycles 3 to 14): From Cycle 3, a 4-week dose ramp-up (one week at each dose of 20 mg, 50 mg, 100 mg, and 200 mg once daily) followed by 400 mg once daily until the end of Cycle 14
Comparator*	IV: Ibrutinib (Cycles 1 to 15): 420 mg orally once daily Venetoclax (Cycles 4 to 15): From Cycle 4, a 4-week dose ramp-up (one week at each dose of 20 mg, 50 mg, 100 mg, and 200 mg once daily) followed by 400 mg once daily until the end of Cycle 15 VO: Venetoclax (Cycles 1 to 12): From Cycle 1 Day 22, a 4-week dose ramp-up (one week at each dose of 20 mg, 50 mg, 100 mg, and 200 mg once daily) followed by 400 mg once daily until the end of Cycle 12 Obinutuzumab (Cycles 1 to 6): From Cycle 1 Day 1, a 4-week dose ramp-up (Day 1, 100 mg; Day 2, 900 mg; Days 8 and 15, 1000 mg) followed by 1000 mg given on Day 1 of each cycle by intravenous infusion
Outcomes	PFS, OS, TTNT, AEs
Clinical claim	In patients with previously untreated CLL/SLL, FD AV is non-inferior in terms of efficacy with superior safety compared to IV. In patients with previously untreated CLL/SLL, FD AV is non-inferior in terms of efficacy with a more favourable safety profile compared to VO.

Source: Table 1-1, pp2-3 of the submission.

AE, adverse event; AV, acalabrutinib+venetoclax; CLL, chronic lymphocytic leukaemia; FD, fixed duration; IV, ibrutinib+venetoclax; OS, overall survival; PFS, progression free survival; SLL, small lymphocytic lymphoma; TTNT, time to next treatment; VO, venetoclax+obinutuzumab.

* All cycles are for 28 days

2 Background

Registration status

2.1 Acalabrutinib was TGA registered on 22 November 2019 for "the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)" when administered continuously (100 mg twice daily) until disease progression (i.e. treat to progression [TTP] regimen). Due to the proposed changes to the circumstances of use (the proposed FD regimen and use in combination with venetoclax), at the time of the evaluation, acalabrutinib was under evaluation by the TGA for the following extension of indication:

- "CALQUENCE in combination with venetoclax with or without obinutuzumab is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)."

2.2 The TGA Clinical Evaluation Report (Round 2) was available at the time of PBAC consideration. The TGA Delegate's Overview was not available prior to the PBAC meeting.

Previous PBAC consideration

2.3 Acalabrutinib, either as monotherapy or in combination with obinutuzumab (A±O), was PBS listed on 1 January 2024 for the treatment of previously untreated CLL/SLL when administered as a TTP regimen. The PBAC recommended listing of A±O TTP regimen on a cost-minimisation basis to VO FD regimen and zanubrutinib TTP regimen at the July 2023 PBAC Meeting. Acalabrutinib is also currently PBS listed for relapsed/refractory CLL (since 1 September 2020) and relapsed/refractory mantle cell lymphoma (since 1 February 2022).

2.4 The PBAC has not previously considered acalabrutinib, for use in combination with venetoclax (AV), as a FD regimen for the treatment of previously untreated CLL/SLL.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
Initial treatment Acalabrutinib 100 mg tablet, 56	$7414.90 published price $[redacted] effective price	1	56	1	Calquence
Continuing treatment Acalabrutinib 100 mg tablet, 56	$7414.90 published price $[redacted] effective price	1	56	5	Calquence
Category / Program: General Schedule					
Prescriber type: ☒ Medical Practitioners					
Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)					
Severity: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Initial treatment in first-line therapy (treatment cycles 1 to 2 inclusive)					
Clinical criteria:					
The condition must be untreated with drug treatment at the time of the first dose of this drug; OR Patient must have developed an intolerance of a severity necessitating permanent treatment withdrawal following use of another drug PBS indicated as first-line drug treatment of CLL/SLL **AND** The treatment must only be prescribed for a patient with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition **AND** The treatment must be in combination with venetoclax (refer to Product Information for timing of acalabrutinib and venetoclax doses)					
Administrative Advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy - see 'Indications for treatment' section; and (2) recognising progressive disease - see 'Definition of response, relapse, and refractory disease' section. See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.					
Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.					
Treatment Phase: Continuing treatment (treatment cycles 3 to 14 inclusive) of first-line therapy					
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition **AND** The treatment must be in combination with venetoclax (refer to Product Information for timing of acalabrutinib and venetoclax doses) **AND** The treatment must cease upon disease progression; OR The treatment must cease upon completion of 14 cycles of treatment with this drug for this condition, whichever comes first.					
Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.					

Source: Table 1-11, 1-12, 1-13, 1-14, p21-24 of the submission.

3.1 The submission requested a Special Pricing Arrangement (SPA) for acalabrutinib in this indication, consisting of a published AEMP of $7,251.97 (published DPMQ of

$7,414.90) and an effective AEMP of $[redacted] (effective DPMQ of $[redacted]). The proposed SPA would maintain the same published price per box as the current PBS listing of acalabrutinib, when used as part of the A±O regimen for previously untreated CLL/SLL, but represents an increase in the effective price (the current effective AEMP is $[redacted] per box) due to the shorter average treatment duration with the FD regimen (~13 months) compared to the TTP regimen (~50 months).

3.2 The submission requested Authority Required – Telephone/electronic (via Online PBS Authorities) listings for both initial/grandfathering and continuing treatment, noting that this would be consistent with existing acalabrutinib listings in the R/R setting, and with VO in the first-line setting. The Secretariat suggested that alternatively, an Authority Required – Written assessment listing could be appropriate for the continuing treatment restriction (treatment cycles 3 to 14 inclusive) of first-line therapy, to help ensure that acalabrutinib is not being administered as monotherapy. The Pre-Sub-Committee Response (PSCR) considered this requirement unnecessary, asserting that there would be a low risk of clinicians prescribing acalabrutinib as monotherapy using the proposed restriction. In support of this assertion, the PSCR stated that there "is no clinical evidence supporting the use of acalabrutinib monotherapy as a FD regimen in first-line CLL/SLL therapy, and this is not reflected in current practice or guidelines".

3.3 At the proposed recommended FD dosing regimen, initial treatment would provide up to 56 days of treatment when acalabrutinib is given as monotherapy (Cycles 1-2), and continuing treatment would provide up to 6 months of treatment per prescription (original plus 5 repeats), with patients requiring two prescriptions to complete the remaining 12 cycles (Cycles 3-14). The maximum quantity and number of repeats are appropriate for this indication.

3.4 The proposed restriction criteria for acalabrutinib were consistent with the current criteria of other PBS-listed treatments for the treatment of patients with previously untreated CLL/SLL. Eligible patients must have previously untreated and active disease, defined by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (latest version), and treatment must be in combination with venetoclax. Patients must cease treatment upon completion of 14 cycles of treatment with acalabrutinib or upon disease progression, whichever comes first. In addition, the submission proposed flow on changes to the current PBS listing of venetoclax to allow treatment in combination with acalabrutinib.

3.5 Although consistent with other PBS-listed treatments, the proposed listing was narrower than the proposed TGA indication in terms of circumstances of use, which includes combination treatment of AV with or without obinutuzumab, but broader than the primary clinical evidence in terms of the proposed eligible population. The AMPLIFY trial only recruited a 'fit' population (Eastern Cooperative Oncology Group [ECOG] performance status 0-2, few or mild comorbidities, adequate renal function) without del(17p) or *TP53* mutations. The proposed listing does not restrict the eligible population based on Cumulative Illness Rating Scale (CIRS) score and/or creatinine

clearance, consistent with previous PBAC advice that "it would be more clinically appropriate for clinicians/patients to decide the most appropriate treatment regimen for a particular patient, which may involve consideration of a broader range of factors including biological characteristics of the disease and an individual's specific organ sensitivities (e.g. cardiac or renal risk)" (para 7.4, acalabrutinib Public Summary Document [PSD], December 2022 PBAC meeting).

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

4 Population and disease

4.1 CLL is characterised by the proliferation and accumulation of functionally incompetent B lymphocytes in peripheral blood, bone marrow and lymphoid organs. CLL and SLL are considered the same disease with different manifestations. CLL manifests primarily in the blood, whereas when malignant cells are primarily in lymph nodes, the disease is classified as SLL. Treatment pathways for CLL and SLL are the same. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating and unintentional weight loss. In general, patients with asymptomatic early-stage disease, and selected patients with later-stage disease can be monitored without therapy until they have evidence of progressive or symptomatic disease (Hallek et al., 2018). The choice of therapy depends on several factors, including age, fitness, comorbidities, the presence of prognostic genetic mutations, and goals of therapy.

4.2 Acalabrutinib is an orally administered selective small-molecule second-generation Bruton's tyrosine kinase (BTK) inhibitor. Over signalling of BTK may contribute to B cell malignancies, such as CLL. As a second-generation BTK inhibitor, acalabrutinib is more selective in target binding when compared to the first-generation BTK inhibitor ibrutinib, causing fewer side effects. The AV treatment regimen is the first combination of a second-generation BTKi with venetoclax. Venetoclax is a selective, orally bioavailable small-molecule BCL-2 inhibitor. BCL-2 is overexpressed in CLL cells, where it mediates tumour cell survival by blocking programmed cell death, causing resistance to chemotherapeutics.

4.3 The submission positioned AV as an all-oral alternative treatment option to the available PBS-listed treatment options for previously untreated CLL/SLL, including other FD regimens (IV, and VO) as well as TTP regimens (zanubrutinib, and A±O). The use of AV in this setting was consistent with latest NCCN, ESMO and Australian consensus guidelines, which use fitness and genetic features to direct therapy but recommend BTK inhibitors in all populations.

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

5 Comparator

5.1 The submission nominated IV and VO as relevant comparators. The main argument provided in support of this nomination was that IV and VO are FD regimens currently

PBS listed for previously untreated CLL/SLL. The submission also identified zanubrutinib and A±O as potential comparators, which are also PBS listed for previously untreated CLL/SLL but use a TTP dosing strategy. The submission stated that only current FD regimens were nominated as comparators, both for simplicity and because the treatment pathway favours FD dosing compared to TTP (implying doctors first decide upon dosing strategy before treatment). The submission noted that zanubrutinib and A±O were each recommended on the basis of a cost-minimisation approach versus VO, in March 2023 and July 2023 respectively.

5.2 The submission argued that AV (an all-oral regimen) was expected to largely replace IV (an all-oral regimen) due to its safety profile, and that it will also replace VO (an oral + intravenous infusion regimen) to some extent due to the convenience of the all-oral formulation. This argument was poorly justified. While AV and IV are more easily interchangeable as they are both all oral regimens, VO is more established as a treatment option and may have more scope for replacement. A similar argument could also be made for substitution away from the TTP regimens (e.g. zanubrutinib and A±O) due to the more convenient shorter duration of treatment with the FD regimens. Given the recent listing of IV (recommended in March 2024) and A±O (recommended in July 2023), the current treatment patterns for previously untreated CLL/SLL are unclear, reflecting an immature and evolving market.

5.3 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. If the committee is so satisfied, it must make a statement to this effect. For the requested population, both the FD treatments (IV and VO) and the TTP treatments (zanubrutinib and A±O) may be considered alternative therapies because they could be replaced in practice. A comparison of costs between all four of the alternative therapies was conducted during the evaluation.

5.4 Recently published abstracts found zanubrutinib had a favourable progression free survival (PFS) over AV (via network meta-analysis (Shadman et al., 2025): HR 0.41, 95% CI 0.25-0.67; via matching-adjusted indirect treatment comparison (MAIC) (Munir et al., 2025): HR 0.23, 95% CI 0.12-0.48). These results should be interpreted with caution considering the limitations and assumptions of NMA and MAIC methodologies, noting the studies have not been published in full peer-reviewed form.

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 Lymphoma Australia and Rare Cancers Australia via the Consumer Comments facility on the PBS website. The comments were supportive of listing, stating that there is patient preference for targeted time-limited therapies.

Clinical trials

6.3 No head-to-head trials comparing AV to the nominated comparators in the proposed population were identified. In the absence of head-to-head evidence, the submission was based on indirect evidence from six trials/studies:

- One RCT comparing AV vs fludarabine, cyclophosphamide and rituximab (FCR)/ bendamustine and rituximab (BR) in 'fit' patients (AMPLIFY)
- Two RCTs comparing VO vs FCR/BR in 'fit' patients (CLL13 and CRISTALLO)
- One RCT comparing VO vs chlorambucil and obinutuzumab (ChIO) in 'unfit' patients (CLL14)
- One RCT comparing IV to ChIO in 'unfit' patients (GLOW)
- One single arm study of IV in 'fit' patients (CAPTIVATE)

6.4 The main analysis presented in the submission was an anchored indirect comparison of AV (AMPLIFY) versus VO (CLL13 and CRISTALLO) using FCR/BR as the common comparator in a 'fit' population. AMPLIFY and CLL13 formed the primary evidence base, as limited data was available from CRISTALLO (abstract only publication). This approach provided the most robust and reliable comparison given the evidence available, which was for a subset of the proposed PBS population.

6.5 To provide comparison between AV versus VO as well as IV, in a broader population aligned with the proposed PBS restriction (i.e. 'unfit' and 'fit' patients), the submission also presented as supportive analyses: (i) an unanchored (naïve) indirect comparison and (ii) an unanchored simulated treatment comparison (STC). Both methods compared efficacy outcomes between AV (AMPLIFY) versus IV (GLOW and CAPTIVATE), and versus VO (CLL14). While the unanchored (naïve) indirect comparison did not account for differences between the trials that may explain differences in outcomes, the unanchored STC attempted to adjust for differences in baseline characteristics but relied on strong assumptions including no unmeasured confounding and out-of-sample extrapolation. The submission stated that a MAIC was not feasible due to limited overlap between AMPLIFY and supplementary trial populations.

6.6 Details of the trial reports presented in the submission are provided in **Table 2**.

Table 2: Trials and key associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
AMPLIFY (NCT03836261)	AMPLIFY (ACE-CL-311) Interim CSR. 16 September 2024. A Randomized, Multicentre, Open-Label, Phase 3 Study to Compare the Efficacy and Safety of Acalabrutinib (ACP-196) in Combination with Venetoclax with and without Obinutuzumab Compared to Investigator's Choice of Chemoimmunotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Without del(17p) or TP53 Mutation (AMPLIFY) Brown JR, Seymour JF, Jurczak W et al. Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia.	September 2024 NEJM 2025; 392(8): 748-762.
CLL13 (NCT02950051)	Eichhorst, B., C.U. Niemann, A.P. Kater, et al., First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia.	NEJM 2023; 388(19): 1739-1754.
CRISTALLO (NCT04285567)	Sharman, J.P., L. Laurenti, E. Ferrant, et al., CRISTALLO: Results from a Phase III Trial of Venetoclax-Obinutuzumab Versus Fludarabine, Cyclophosphamide and Rituximab or Bendamustine–Rituximab in Patients with Untreated Chronic Lymphocytic Leukemia without Del(17p) or TP53 Mutations	Blood 2024; 144 (Supplement 1): 3237.
CLL14 (NCT02242942)	Fischer, K., O. Al-Sawaf, J. Bahlo, et al., Venetoclax and obinutuzumab in patients with CLL and coexisting conditions.	NEJM 2019; 380(23): 2225-2236.
GLOW (NCT03462719)	Kater, A.P., C. Owen, C. Moreno, et al., Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities.	NEJM Evid 2022; 1(7).
CAPTIVATE (NCT02910583)	Tam, C.S., J.N. Allan, T. Siddiqi, et al., Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort.	Blood 2022; 139(22): 3278-3289.

Source: Table 2-7, pp45-46 of the submission.

6.7 The key features of the AMPLIFY, CLL13, CRISTALLO, CLL14, GLOW and CAPTIVATE are summarised in Table 3.

Table 3: Key features of the included evidence

Trial (date range)[a]	N[b]	Design/ duration	Risk of bias	Patient population	Outcome(s)
AV vs FCR/BR					
AMPLIFY (2019-2024)	581	PIII, R, MC, OL 24-56 wks	Unclear	1L CLL, without del(17p) or TP53 mutation, ≥18 yo, ECOG≤2, CIRS<6, CrCl≥50 mL/min	1º: PFS-IRC; 2º: MRD negativity, OS, ORR, TTNT
VO vs FCR/BR					
CLL13 (2016-2023)	458	PIII, R, MC, OL 24-144 wks	Unclear	1L CLL, without del(17p) or *TP53* mutation, ≥18 yo, ECOG≤2, CIRS<6, CrCl≥70 mL/min	1º: MRD, PFS; 2º: CR, TTNT, OS
CRISTALLO (2020-2024)	166	PIII, R, MC, OL 24 wks	Unclear	1L CLL, without del(17p) or *TP53* mutation, ≥18 yo, CIRS≤6, CrCl≥70 mL/min	1º: MRD; 2º: PFS, CR
VO vs ChlO					
CLL14 (2014-2022)	432	PIII, R, MC, OL 48 wks	Unclear	1L CLL, coexisting medical conditions, CIRS>6 or CrCl<70 mL/min	1º: PFS-IA; 2º: PFS-IRC, OS, CR, TTNT, MRD negativity
IV vs ChlO					
GLOW (2018-2023)	211	PIII, R, MC, OL 24-60 wks	Unclear	1L CLL, ≥65 yo or 18–64 yo with comorbidities, without del(17p) or *TP53* mutation	1º: PFS-IRC; 2º: MRD negativity, CRR, ORR, OS, TTNT
IV					
CAPTIVATE (2016-2023)	159	PII, OL 60 wks	High	1L CLL, ≤70 yo, ECOG≤2, adequate renal function	CR, PFS, OS, ORR, MRD negativity

Source: Table 2-9, p50, Table 2-16, p64 of the submission.
AV=acalabrutinib+venetoclax; BR=bendamustine+rituximab; ChlO= chlorambucil+obinutuzumab; CIRS=Cumulative Illness Rating Scale score; CLL=chronic lymphocytic leukemia; CR=complete response; CrCl=creatinine clearance; CRR=complete response rate; ECOG=Eastern Cooperative Oncology Group performance score; FCR=fludarabine + cyclophosphamide + rituximab; IA=investigator assessed; IRC=Independent Review Committee; MC=multi-centre; MRD=minimal residual disease; OL=open label; ORR=overall response rate; OS=overall survival; PII=phase 2; PIII=phase 3; PFS=progression-free survival; R=randomised; TTNT=time to next treatment for CLL; VO=venetoclax+obinutuzumab; wks=weeks; yo=years old.
[a] Date range from trial start to DCO used in the submission.
[b] N for trial arms relevant to this submission only.

6.8 Overall, the risk of bias of the included trials was unclear due to the open-label nature of the study designs. Blinding was not feasible due to the differences in modes of administration between study treatments (often oral vs intravenous infusion); however, central randomisation was used to reduce potential bias. The primary outcome was also assessed by a blinded independent review committee (IRC) in AMPLIFY and GLOW. There is potential bias when investigators who assess outcomes are aware of treatment assignment, as in CLL13, CLL14 and CAPTIVATE, which may have influenced the treatment of patients in the trial.

6.9 There were differences in eligibility criteria between the trials. AMPLIFY, CLL13, and CRISTALLO were multicentre (AMPLIFY with sites in Australia), randomised, open-label trials that enrolled a 'fit' CLL population with few comorbidities (Cumulative Illness Rating Scale (CIRS) score ≤6), adequate renal function, and without del(17p) or *TP53* mutations. Similarly, CAPTIVATE enrolled a 'fit' population but did not exclude people with del(17p) or *TP53* mutations. CLL14 and GLOW enrolled 'unfit' populations who were older with comorbidities or lower renal function. CLL14 did not exclude people with del(17p) or *TP53* mutations, while GLOW did.

6.10 Based on the baseline characteristics, the patients enrolled in AMPLIFY, CLL13 and CRISTALLO were generally comparable. AMPLIFY had a smaller proportion of patients over 65 years old (27% vs 35% and 34% for CLL13 and CRISTALLO, respectively) and a

smaller proportion of male patients (62% vs 73% and 68%), but patients were similar in Rai stage, IGHV mutation status, and time from diagnosis to trial entry.

Comparative effectiveness

Anchored (Bucher) ITC: AV versus VO

6.11 Table 4 presents the results of the anchored (Bucher) ITC, comparing AV versus VO using FCR/BR as a common comparator in 'fit' patients with previously untreated CLL/SLL, in terms of investigator-reported progression-free survival (PFS-IA), overall survival (OS), and time to next treatment (TTNT).

Table 4: Results for the anchored (Bucher) ITC: PFS-IA, OS, and TTNT in AMPLIFY (AV, 'fit' patients) vs CLL13 (VO, 'fit' patents), and PFS-IA in AMPLIFY (AV, 'fit' patients) vs CRISTALLO (VO, 'fit' patents)

Trial	Outcome	Intervention (AV/VO) n/N (%)	Comparator (FCR/BR) n/N (%)	Absolute difference	HR (95% CI)
PFS-IA					
AMPLIFY (Median follow-up: 40.8 mths)	Progressed Median months PFS	78/291 (26.8) NE (51.6, NE)	95/290 (32.8) 48.8 (43.1, NE)	6.0% NE	**0.58 (0.43, 0.78)**
CLL13 (Median follow-up: 50.7 mths)	Progressed Median months PFS	55/229 (24.0) NE (NE, NE)	90/229 (39.3) NE (NE, NE)	15.3% NE	**0.47 (0.34, 0.67)** [a]
CRISTALLO (Median follow-up: 32.0 mths) [b]	Progressed Median months PFS	NR NE (NE, NE)	NR NE (NE, NE)	- NE	0.49 (0.20, 1.30)
ITC: AV (AMPLIFY) vs. VO (CRISTALLO) ITC: AV (AMPLIFY) vs. VO (CLL13)					1.18 (0.44, 3.16) 1.23 (0.81, 1.88)
OS					
AMPLIFY (Median follow-up: 40.8 mths)	Died	18/291 (6.2)	42/290 (14.5)	8.3%	**0.33 (0.18, 0.56)**
	Died (censoring COVID-19 deaths) [c] Median months OS	8/291 (2.7) 57.8 [d] (57.8, NE)	21/290 (7.2) NE	4.5% NE	**0.27 (0.11, 0.60)**
CLL13 (Median follow-up: 50.7 mths)	Died Median months OS	11/229 (4.8) NE	17/229 (7.4) NE	2.6% NE	0.57 (0.27, 1.22) [e]
ITC: AV (AMPLIFY) vs. VO (CLL13) ITC: AV (AMPLIFY, COVID-19 adjusted) vs. VO (CLL13) [f]					0.58 (0.23, 1.49) 0.47 (0.15, 1.47)
TTNT					
AMPLIFY (Median follow-up: 40.8 mths)	Initiated next Tx Median months TTNT	52/291 (17.9) NE	84/290 (29.0) NE	11.1% 54.8 (48.6, NE)	**0.45 (0.32, 0.64)**
CLL13 (Median follow-up: 50.7 mths)	Initiated next Tx Median months TTNT	NR NE	54/229 (23.6) NE	NE NE	**0.34 (0.23, 0.58)** [a]
ITC: AV (AMPLIFY) vs. VO (CLL13)					1.32 (0.74, 2.36)

Bold indicates statistically significant results.

Source: Compiled during the evaluation from Table 2.32 and Table 2-33, p101 and Table 2.36, p104 of the submission and Table 24, p105 of AMPLIFY CSR (Sep24).

AV=acalabrutinib+venetoclax; BR=bendamustine+rituximab; FCR=fludarabine+cyclophosphamide+rituximab; HR=hazard ratio; IA=investigator assessed; ITC=indirect treatment comparison; mths=months; NE=not estimable; OS=overall survival; PFS=progression free survival; TTNT=time to next treatment; Tx=treatment; VO=venetoclax+obinutuzumab.

[a] Converted 97.5% CI to 95% CI using z-scores.

[b] CRISTALLO was immature at the March 19, 2024 data cut-off, with only 32 months of follow-up. At this data cut-off, Sharman J.P. et al., 2024 reported that PFS remained immature, with 2-year PFS rates of 95.7% in the AV arm and 90.4% in the VO arm.

[c] AMPLIFY was conducted during the COVID-19 era therefore a sensitivity analysis was conducted to assess the potential impact of COVID-19 deaths on OS, by censoring COVID-19 deaths (page 105, AMPLIFY CSR, Sep24). The hazard ratio for this analysis assumed COVID-19 deaths were independent of both treatment and outcomes, which may not be reasonable. Death due to COVID-19 is a competing risk and likely related to patient comorbidities and treatment-related effects (e.g., the level of immunosuppression). In AMPLIFY, there were more COVID-19 deaths in the control arm suggesting COVID-19 deaths were not independent, but the relative treatment effect was robust to censoring because a similar proportion of deaths were due to COVID-19 in both arms.

[d] Median OS estimate for AV arm is unstable due to low number of patients at risk.

[e] HR calculated for the submission using the log-rank test approximation.

[f] Estimated during the evaluation.

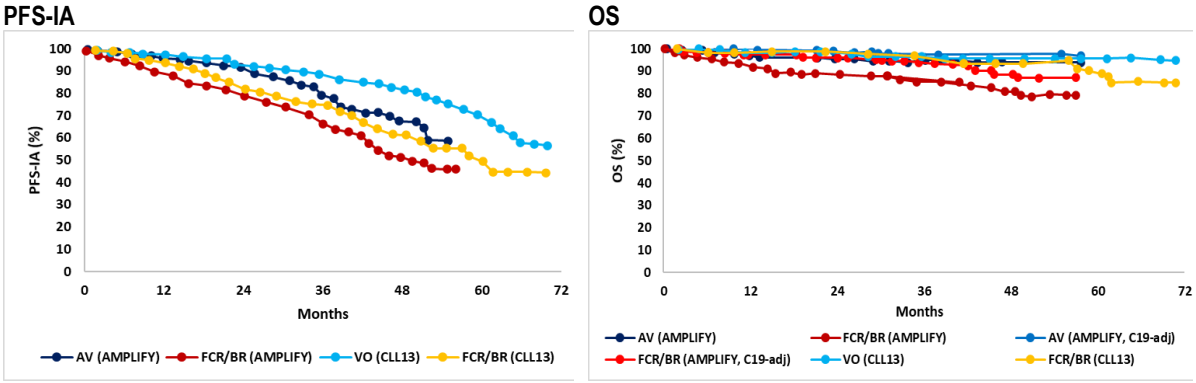
6.12 The anchored ITC suggested no statistically significant difference between AV and VO for PFS-IA (HR 1.23; 95%CI: 0.81, 1.88), OS (HR 0.58; 95%CI: 0.23, 1.49) or TTNT (HR=1.32; 95%CI: 0.74, 2.36), in patients 'fit' for FCR/BR. The submission did not propose a non-inferiority margin as there was no established non-inferiority margin for previously untreated CLL/SLL. A non-inferiority margin was not proposed for PFS or OS in the zanubrutinib CLL submission (para 6.41, zanubrutinib PSD, March 2023

PBAC meeting) nor the ibrutinib CLL submission (para 6.45, ibrutinib PSD, March 2024 PBAC meeting).

6.13 The results for OS were considered highly imprecise given the low number of events in each trial arm and the high proportion of deaths reported in AMPLIFY due to COVID-19. Although AMPLIFY (2019-2024) was conducted later than CLL13 (2016-2019), a period when more subsequent-line therapies were available and could have been expected to improve OS, the baseline mortality rate was higher. The AMPLIFY CSR reported that "the majority of deaths in all arms were attributable to AEs, most of which were confirmed or suspected COVID-19 AEs."

6.14 Figure 1 presents the Kaplan-Meier (KM) curves for PFS-IA and OS reported in AMPLIFY and CLL13, including the results of a sensitivity analysis after censoring COVID-19 deaths in AMPLIFY. After the COVID-19 adjustment, the absolute survival benefit with AV versus FCR/BR was largely reduced (Figure 1) despite producing a similar hazard ratio (and similar indirect hazard ratio) due to the low number of events in the comparator arm and similar proportion of deaths due to COVID-19 in both arms.

Figure 1: Results of PFS-IA and OS across AMPLIFY and CLL13



Source: Constructed during the evaluation using Figure 2-8, p80, Figure 2-9, p80, Figure 2-14, p86, Figure 2-15, p86, and 2-22, p98 of the submission.

AV=acalabrutinib+venetoclax; BR=bendamustine+rituximab; ChlO=chlorambucil+obinutuzumab; C19-adj=COVID-19-adjusted; FCR=fludarabine+cyclophosphamide+rituximab; IA=investigator assessed; OS=overall survival; PFS=progression free survival; VO=venetoclax+obinutuzumab.

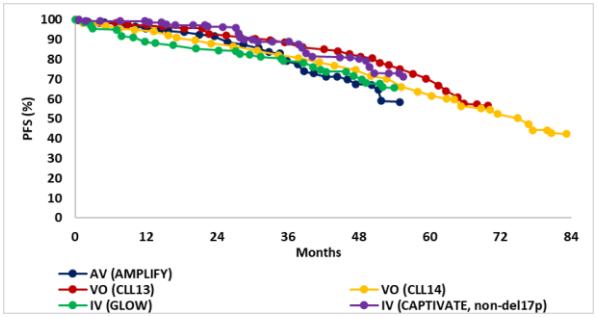
Note: Survival outcomes from CRISTALLO were not presented in the submission and are therefore not shown in the figure above. Neither the submission nor the AMPLIFY CSR reported TTNT Kaplan-Meier curves.

Unanchored (Naïve) ITC and STC: AV versus VO and IV

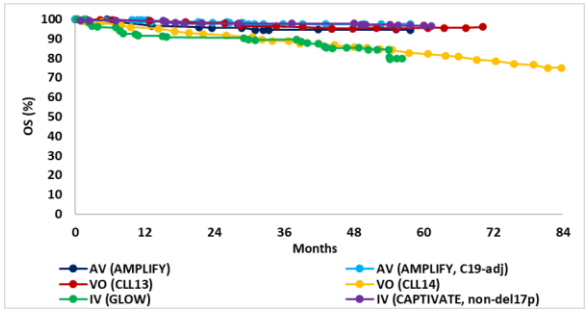
6.15 Figure 2, constructed during the evaluation, presents the results of the unanchored (naïve) indirect comparison of the AV (AMPLIFY) versus VO (CLL14) and IV (GLOW and CAPTIVATE). The COVID–adjusted survival outcomes for AV (AMPLIFY) and for VO (CLL13) were presented in this Figure only for visual comparison.

Figure 2: Naïve comparison of PFS-IA and OS, in AMPLIFY (AV; 'fit' patents), GLOW (IV, 'unfit' patients), CAPTIVATE (IV, 'unfit' patients) and CLL14 (VO, 'unfit' patients)

PFS-IA



OS



Source: Constructed during the evaluation using Figure 2-8, p80, Figure 2-10, p81, Figure 2-11, p81, Figure 2-12, p82, Figure 2-14, p86, Figure 2-16, p87, Figure 2-17, p87, and Figure 2-18, p88 of the submission.

AV=acalabrutinib+venetoclax; IA=investigator assessed; IV=ibrutinib+venetoclax; OS=overall survival; PFS=progression free survival; VO=venetoclax+obinutuzumab.

Note: AMPLIFY-COVID–adjusted and CLL13 survival curves are presented for visual comparison only; they were not included in the submission's unanchored ITC.

6.16 Across the trials, PFS-IA at 48 months was 67.3% for AV, 69.7% to 78.5% for IV, and 74.0% for VO. Similarly, OS at 48 months was 94.1% for AV, 85.5% to 98.1% for IV, and 85.4% for VO. The submission acknowledged the notable differences between the trials in terms of patient demographics, disease characteristics, timing with COVID-19, and outcome assessment criteria, which could likely reduce the transitivity between the trials and limit the validity of the conclusions.

6.17 Table 5 presents the results of the STC. The results were generated by fitting parametric survival models to AMPLIFY individual patient data (IPD) to estimate the association between baseline characteristics and outcomes (PFS-IRC blinded and OS). The best fitting model was then used to estimate the outcomes of AV that would have been observed for patients enrolled in the comparator trials. Restricted mean survival time (RMST, in months), corresponding to the area under the survival curve, was estimated at the point of the minimum of the longest follow-up times between the two trials. For each comparison, the models only included baseline characteristics reported in both trials and the best fitting function was chosen using the Akaike information criterion (AIC).

Table 5: RMST difference (months) for best-fitting models for PFS-Blinded IRC and OS – STC

Comparator study	Distribution	Endpoint	RMST diff (95% CI)
CAPTIVATE+GLOW (IV)	Gompertz	PFS	-2.2 (-4.9, 0.6)
GLOW (IV)	Gompertz		0.9 (-5.5, 7.2)
CLL14 (VO)	Gompertz		0.4 (-5.0, 5.7)
CAPTIVATE+GLOW (IV)	Gompertz	PFS C19	-1.0 (-3.6, 1.5)
GLOW (IV)	Gompertz		3.3 (-2.5, 9.0)
CLL14 (VO)	Gompertz		2.9 (-1.5, 7.3)
CAPTIVATE+GLOW (IV)	Gompertz	OS	0.2 (-1.7, 2.1)
GLOW (IV)	Gompertz		-1.1 (-11.5, 9.2)
CLL14 (VO)	Gompertz		-0.4 (-9.5, 8.8)
CAPTIVATE+GLOW (IV)	Exponential	OS C19	**2.0 (0.4, 3.7)**
GLOW (IV)	Exponential		4.5 (-2.5, 11.6)
CLL14 (VO)	Exponential		**4.9 (0.4, 9.3)**

Bold indicates statistically significant results.
Source: Table 2.43, p113 of the submission.
AV=acalabrutinib+venetoclax; C19=COVID-19; Diff=difference; IRC=Independent Review Committee; IV=ibrutinib+venetoclax; OS=overall survival; PFS=progression free survival; RMST= restricted mean survival time; STC= simulated treatment comparison; VO=venetoclax+obinutuzumab.

6.18 The results of the STC generally showed no statistically significant differences between AV versus IV and VO in terms of PFS RMST or OS RMST, after adjusting for differences in patient characteristics across the trials. The one exception was STC using AMPLIFY data adjusted for COVID-19 deaths, which showed a significant improvement in OS for AV versus VO and IV.

6.19 The STC was considered highly uncertain and should be interpreted with caution for the following reasons:

- there was a lack of transparency in reporting, with no detail provided in the submission on the number of parametric functions tested, the covariates included in the final model, the regression coefficients, the predictive performance or the method used to estimate confidence intervals;
- the analysis was unlikely to control for all important prognostic factors, given the limited number of common covariates across the trials, which is a key assumption of the methodology.
- the limited population overlap between AMPLIFY and comparator trials, which increases uncertainty due to out-of-sample extrapolation, which is another key assumption of the methodology; and
- the COVID-19 adjusted analysis was considered highly uncertain due to the very small number of covariates included, 'chosen' without clear justification, and very few deaths in AMPLIFY after COVID censoring (i.e., few degrees of freedom to estimate a robust model). The magnitude of the treatment effect compared to the unadjusted analysis also lacked face validity given very few patients died in the AV arm of AMPLIFY and the COVID adjustment reported in the AMPLIFY CSR had negligible impact on the mortality rate.

Comparative harms

Anchored (Bucher) ITC: AV versus VO

6.20 Table 6 presents the results of an anchored (Bucher) ITC between AV (AMPLIFY) versus VO (CLL13) in terms of safety outcomes.

Table 6: Summary of key adverse events across trials and the results of the anchored ITC: AMPLIFY (AV, 'fit' patients) vs CLL13 (VO, 'fit' patients)

Trial	AMPLIFY [a]		CLL13		OR (95%CI)	RR (95%CI)	Risk Diff % (95%CI)
Arm (N)	AV (291)	FCR/BR (259)	VO (228)	FCR/BR (216)			
AE category, n (%)							
Any AE	270 (92.8)	236 (91.1)	214 (93.9)	204 (94.4)	1.39 (0.51, 3.81)	1.02 (0.96, 1.10)	2.2 (-4.1,8.6)
Grade ≥3 AE [b]	156 (53.6)	157 (60.6)	183 (80.3)	166 (76.9)	0.61 (0.35,1.08)	0.85 (0.71,1.01)	-10.4 (-21.7,0.8)
SAE	72 (24.7)	71 (27.4)	108 (47.4)	116 (53.7)	1.12 (0.66,1.91)	1.02 (0.73,1.43)	3.7 (-8.2,15.5)
Death for AE	10 (3.4)	9 (3.5)	9 (3.9)	16 (7.4)	1.92 (0.56,6.67)	1.86 (0.56,6.10)	3.4 (-1.9,8.7)
Discont for AE [c]	23 (7.9)	28 (10.8)	13 (5.7)	43 (19.9)	**2.91 (1.22, 6.96)**	**2.55 (1.16, 5.63)**	**11.3 (3.5,19.1)**
AESI (Grade ≥ 3, prevalence ≥ 5%)							
Anaemia	11 (3.8)	17 (6.6)	11 (4.8)	16 (7.4)	0.88 (0.29, 2.68)	0.88 (0.31, 2.53)	-0.2 (-6.0,5.6)
Leukopenia	95 (32.6)	120 (46.3)	13 (5.7)	26 (12.0)	1.27 (0.59, 2.76)	1.49 (0.76, 2.92)	-7.4 (-17.0,2.3)
Neutropenia	94 (32.3)	112 (43.2)	103 (45.2)	98 (45.4)	0.63 (0.38, 1.05)	0.75 (0.56, 1.01)	-10.7 (-23.0,1.5)
Other leukopenia	6 (2.1)	16 (6.2)	NR	NR	NR	NR	NR
Thrombocytopenia	6 (2.1)	28 (10.8)	34 (14.9)	18 (8.3)	0.09 (0.03, 0.27)	0.11 (0.04, 0.30)	-15.3 (-22.5,-8.1)
Infections	36 (12.4)	26 (10.0)	30 (13.2)	40 (18.5)	1.90 (0.90, 3.99)	1.73 (0.91, 3.31)	7.7 (-0.9,16.3)
TLS [d]	1 (0.3)	8 (3.1)	19 (8.3)	9 (4.2)	**0.05 (0.01,0.49)**	**0.06 (0.01,0.51)**	**-6.9 (-11.9,-1.9)**

Source: Compiled during the evaluation from Table 2.19, p67, Table 2-29, p91, Table 2-30, pp92-93 and Table 2.35, pp102-103 of the submission of the submission, and estimated using Attachment 2.9-Anchored ITC AV vs VO of the submission.

A= acalabrutinib; AE=adverse event; AESI=adverse event of special interest; AV=acalabrutinib+venetoclax; BR=bendamustine+rituximab; C=cyclophosphamide; CI=confidence interval; Diff=difference; Discont=discontinue; DoE=duration of exposure; F=fludarabine; FCR=fludarabine+cyclophosphamide+rituximab; HR=hazard ratio; mths=months; N=number of patients; NR=not reported; OR=odds ratio; R= rituximab; RDI=relative dose intensity; RR=relative risk; SAE=serious adverse event; SAS=safety analysis set; sub=subgroup; TEAE=treatment-emergent adverse event; TLS= Tumour lysis syndrome; V=venetoclax; VO=venetoclax+obinutuzumab.

[a] Results are from the safety population set, data cut-off: September 2024.

[b] Grade 3 or 4 for the CLL-14 trial.

[c] Discontinuation of any drug due to adverse events.

[d] Any grade TLS was reported to be OR=0.04 (0.005, 0.39), RR=0.05 (0.01, 0.42), and Risk Difference=-9.1% (-14.5%, -3.7%).

6.21 The results of the anchored (Bucher) ITC found that AV and VO had similar rates of serious AEs, Grade ≥3 AEs and AEs leading to death, but patients treated with AV were statistically significantly less likely to develop Grade≥3 tumour lysis syndrome (TLS) (Risk Difference=-6.9%). The submission argued that potential confounding factors related to COVID-era recruitment and the more sensitive CTCAE v5.0 AE reporting in AMPLIFY, may bias against AMPLIFY and in favour of CLL13 results in an indirect treatment comparison.

Unanchored (Naïve) ITC: AV versus VO and IV

6.22 The results of a separate unanchored (naïve) indirect comparison of safety outcomes presented by the submission found that AV (AMPLIFY) demonstrated lower rates of several Grade ≥3 adverse events compared to (i) IV (GLOW and CAPTIVATE) in terms of atrial fibrillation (0.3% vs 7%), hypertension (3% vs 6-8%), and compared to (ii) VO (CLL14) in terms of infection (12% vs 20%), neutropenia (32% vs 53%), tumour lysis

syndrome (0.3% vs 2%), and infusion-related reactions (0% vs 9%). The submission acknowledged the notable differences between the trials in terms of patient demographics, disease characteristics, timing with COVID-19, and AEs outcomes assessment criteria, which could likely reduce the transitivity between the trials and limit the validity of the conclusions.

Benefits/harms

6.23 A benefits and harms table was not presented as the submission made a claim of non-inferiority in terms of effectiveness, with no meaningful differences between AV versus VO and IV in terms of PFS or OS. For safety outcomes, a quantitative comparison between AV and IV was not possible based on the evidence available. However, on the basis of indirect evidence presented in the submission, for every 100 patients treated with AV in comparison with VO, approximately 6.9 fewer patients would experience Grade ≥3 TLS.

Clinical claim

6.24 The submission described AV as non-inferior in terms of effectiveness compared with IV and VO, superior in terms of safety compared to IV and more favourable in terms of safety compared to VO.

6.25 On balance, the evaluation considered the clinical claim of non-inferior effectiveness was adequately supported by the evidence presented in the submission. The anchored (Bucher) ITC found no statistically significant difference between AV and VO in terms of PFS and OS in 'fit' patients. This finding was supported by the unanchored ITC that found no difference between AV and VO or IV, assuming use in unfit patients. (The PBAC previously considered that IV and VO have similar efficacy in previously untreated CLL/SLL (Ibrutinib PSD, March 2024 PBAC meeting) and expanded the current PBS restriction criteria for IV and VO to include 'unfit' patients (Acalabrutinib PSD and Ibrutinib PSD, December 2022 PBAC meeting).)

6.26 The evaluation considered that the clinical claim of superior (or more favourable) safety versus IV and VO was difficult to assess given the evidence available in the submission but was likely reasonable. Compared to VO, the unanchored (naïve) indirect comparison of safety outcomes found lower rates of Grade ≥3 AEs (including severe infection, neutropenia, infusion-related reactions and TLS), but the anchored (Bucher) ITC found no difference in Grade ≥3 AEs except for TLS (although infusion-related reactions were not reported). Only an unanchored (naïve) indirect comparison of safety outcomes was presented for the comparison to IV, finding a more favourable profile versus IV, including significantly fewer Grade≥3 cardiac events (notably atrial fibrillation and hypertension) and lower rates of diarrhoea.

6.27 The PBAC had previously considered a claim of superior safety for A±O compared with VO in first line CLL was not adequately supported but accepted a claim of non-inferior safety (Acalabrutinib PSD, July 2023 PBAC meeting). In the refractory/relapsed CLL/SLL setting, the PBAC had previously considered that the safety of acalabrutinib

monotherapy was likely to be non-inferior to ibrutinib monotherapy (Acalabrutinib PSD, March 2020 PBAC meeting).

6.28 The PBAC considered that the claim of non-inferior comparative effectiveness to IV and to VO was likely reasonable, with some uncertainty.

6.29 The PBAC considered that the claim of superior comparative safety to IV and a more favourable safety profile compared to VO was likely reasonable.

Economic analysis

6.30 The submission presented a cost-minimisation approach (CMA) comparing treatment costs with AV versus VO for patients with previously untreated CLL/SLL. The CMA assumed equivalent total treatment costs for AV and VO, incorporating cost offsets related to the administration of obinutuzumab and a lower incidence of TLS. The submission did not consider the cost of other PBS listed medications for previously untreated CLL/SLL on the assumption that the cost of VO could proxy for other treatments. The CMA was conducted using the effective AEMP of obinutuzumab (which is the same as the published AEMP) and an estimated effective AEMP for venetoclax (the effective AEMP of venetoclax was known to the sponsor prior to a 5% statutory price reduction in April 2024).

6.31 Table 7 summarises the key components and assumptions of the CMA.

Table 7: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	The submission claimed that AV is non-inferior to VO in terms of efficacy, based on the results of the Bucher method ITC. This was appropriate.
Therapeutic claim: safety	The submission claimed that AV has a more favourable safety compared to VO, based on the results of the Bucher method ITC. This was appropriate.
Evidence base	• A Bucher ITC of AV vs VO via the common comparator FCR/BR, using data from AMPLIFY and CLL13 for the outcomes PFS-IA, OS, TTNT and safety, supplemented by CRISTALLO for the key outcome of PFS-IA. • A naïve comparison of AV vs VO, using data from AMPLIFY and CLL14 for the outcomes PFS-IA, OS and safety. • An unanchored STC of AV vs VO, using individual patient data from AMPLIFY and aggregate data from CLL14 for the outcomes PFS and OS.
Equi-effective doses	One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts, equivalent to 12.97 acalabrutinib plus one initial and 9.89 continuing venetoclax scripts.
Direct medicine costs	• Venetoclax initial treatment script (PBS item code: 12188L): $[redacted][a] • Venetoclax continuing treatment script (PBS item codes: 12205J, 12199C): $[redacted][a] • Obinutuzumab (PBS item codes: 12193R for public, 12204H for private): $4,525.52 per script
Other costs or cost offsets	• Venetoclax TLS-related costs: – For VO: $1,410.18; based on estimate in 2023 PBAC zanubrutinib submission adjusted for inflation (para 6.71, zanubrutinib PSD, March 2023 PBAC meeting) – For AV: $1,281.85; assuming RD = - 9.1% (Bucher ITC) • Obinutuzumab administration costs: $1,192.61 for 5.5 infusions with VO, based on 2024 PBAC ibrutinib submission (para 6.79, ibrutinib PSD, March 2024 PBAC meeting); assumes costs for intravenous administration (MBS 13950 $126/infusion), specialist visit (MBS 116; $89.40/infusion), and premedication costs (paracetamol 500 mg × 2, dexamethasone 4 mg × 5, loratadine 10 mg × 1; $1.44/ infusion).

Source: Table 3-1, p129 of the submission.

AEMP=Australian ex-manufacturer price; AV=acalabrutinib + venetoclax; BR=bendamustine + rituximab; CMA=cost-minimisation approach; CLL=chronic lymphocytic leukaemia; FCR=fludarabine + cyclophosphamide + rituximab; FD=fixed duration; ITC=indirect treatment comparison; IV=ibrutinib + venetoclax; OS=overall survival; PBS=Pharmaceutical Benefits Scheme; PFS-IA=investigator assessed progression free survival; SPA=Special Pricing Arrangement; STC=simulated treatment comparison; TLS=tumour lysis syndrome; TTNT=time to next treatment; VO=venetoclax + obinutuzumab.

[a] Estimated effective AEMP, assuming a 5% SPR that occurred in April 2024.

6.32 The equi-effective doses were estimated based on the average number of scripts required for each FD treatment regimen.

- For VO, the average number of scripts per patient course was sourced from the July 2020 PBAC venetoclax submission for previously untreated CLL/SLL: one initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts (para 5.31, venetoclax PSD, July 2020 PBAC meeting).
- For AV, the average number of scripts per patient course was derived using AMPLIFY-reported mean time on treatment (ToT, A: 12.7, V: 10.9) and mean relative dose intensity (RDI, A: 94%, V: 92%). After adjusting for RDI and the 28-day treatment cycle, patients on average received 12.97 acalabrutinib scripts and 10.84 venetoclax scripts per course of treatment.

6.33 The estimated average number of scripts for VO in the July 2020 PBAC venetoclax submission was based on CLL14, which reported a slightly shorter mean duration of treatment compared to CLL13. Although CLL13 was the main comparator trial in the current submission, the use of estimates from CLL14 may have been appropriate for consistency with past costing calculations.

6.34 Table 8 shows the results of the CMA presented in the submission.

Table 8: Results of the cost-minimisation approach (using estimated/proposed effective AEMPs)

Treatments	V (AV)	A (AV)	V (VO)	O (VO)
Drug costs				
Effective AEMP, initial [a]	$	$	$	$4,525.52
Effective AEMP, continuing [a]	$	$	$	$4,525.52
Initial scripts number	1	-	1	-
Continuing scripts number	9.84	12.97	8.67	7.355
Total drug cost	$	$	$	$33,285.20
Total drug cost/patient	$		$	
Administration costs				
Intravenous administration (13950)	$0.00	$0.00	$0.00	$693.00
Specialist visit (116)				$491.70
Premedication costs				$7.91
Total cost	$		$	
Adverse events prophylaxis/ monitoring/ management costs				
TLS cost	$1,281.85	$0.00	$1,410.18	$0.00
Total cost per course	$		$	

Source: Table 3-6, p133 of the submission.

A=acalabrutinib; AEMP=Approved Ex-Manufacturer Price; AV=venetoclax+acalabrutinib; I=ibrutinib; IV=ibrutinib+venetoclax; O=obinutuzumab; PBS=Pharmaceutical Benefits Scheme; TLS=tumour lysis syndrome; V=venetoclax; VO=venetoclax + obinutuzumab.

Note: **X (XZ)** refers to treatment X as part of the XZ regimen.

[a] Estimated effective AEMP, assuming a 5% SPR that occurred in April 2024.

6.35 The total treatment cost per patient per course was estimated as $ for both the AV and VO regimens. Drug costs were approximately % higher with the AV regimen, due to cost offsets related to obinutuzumab administration and TLS prophylaxis and monitoring. Although the magnitude of the reduction in TLS was considered uncertain, excluding TLS-related cost offsets only reduced the proposed AEMP for acalabrutinib by %.

AV Drug cost/patient/course: $

6.36 Table 9 outlines the drug cost per patient for AV, VO, and IV, across the economic model and the financial estimates. Costs are based on the proposed and estimated effective AEMPs.

Table 9: Drug cost per patient for proposed and comparator drugs (using estimated/proposed effective AEMPs)

	AV			VO			IV		
	Trial (AMPLIFY)	CMA	Financial estimates	Trial (CLL14)	CMA	Financial estimates	Trial (GLOW)	CMA	Financial estimates
Cost per script [a]	NR	A: $[redacted], V (initial): $[redacted], V (continuing): $[redacted]		NR	V (initial): $[redacted], V (continuing): $[redacted] O: $4,525.52		NR	NR	V (initial): $[redacted], V(continuing): $[redacted] I: $[redacted] [b]
Compliance	Mean expo: A: 12.7 mths, V: 10.9 mths, RDI: A: 94%, V: 92%.	A: 12.97 scripts, V (initial): 1 script, and V (continuing): 9.84 scripts		Mean expo: V: 9.47 mths, O: NR. RDI: V: NR, O: NR.	V (initial): 1 script, V (continuing): 8.67 scripts, and O: 7.355 scripts		Mean expo: I: 11.89 mths, V: 10.21 mths; RDI: I: 91.0% V: 89.9%.	NR	I: 12.03 scripts, V (initial): 1 script, and V (continuing): 9.39 scripts
Cost/ patient /course [c]	NR	$[redacted]		NR	$[redacted]		NR	NR	$[redacted]

Source: Compiled during the evaluation from Table 3-2, p130, Table 3-6, p133, and Table 4-21, p156 of the submission, Table 7, venetoclax PSD, July 2020 PBAC meeting, Table 16, Ibrutinib PSD, March 2024 PBAC meeting.

A=acalabrutinib; AEMP=Australian ex-manufacturer price; AV=acalabrutinib + venetoclax; CMA=cost-minimisation approach; expo=exposure; IV=ibrutinib + venetoclax; mths=months; NR=not reported; O=obinutuzumab; RDI=relative dose intensity; V=venetoclax; VO=venetoclax + obinutuzumab.

[a] This is based on the proposed or estimated effective AEMPs.

[b] The price of ibrutinib was back calculated by the submission by setting the total cost of the IV regimen equivalent to the total cost of the VO regimen, which included atrial fibrillation monitoring and medication costs associated with IV.

[c] Total costs were calculated based on the effective AEMPs, and administration and adverse event management costs were excluded.

Estimated PBS usage & financial implications

6.37 This submission was not considered by DUSC.

6.38 The submission used a market share approach to estimate the utilisation and financial implications of listing AV on the PBS/RPBS for untreated CLL/SLL. It was assumed that AV would only substitute for other FD regimens (VO and IV) and would not substitute for TTP regimens (A±O and zanubrutinib). This assumption was poorly justified.

6.39 To estimate the size of the current market of FD regimens for untreated CLL/SLL, the submission used venetoclax initiation ramp-up item numbers as a proxy for the number of patients receiving treatment, as the same treatment is common to patients treated with both VO and IV. The historical estimates were extrapolated over six years (2026–2031), and market share assumptions were used to estimate the number of patients treated with each regimen (VO and IV). Script volumes per initiating patient were calculated using equi-effective doses, and then uptake/ substitution rates were applied to estimate the change in the FD market with the proposed listing of AV.

6.40 Table 10 summarises data sources and parameter values used to estimate the utilisation and financial implications.

Table 10: Key inputs for financial estimates (year 1=2026)

<table>
<tr><th>Data</th><th>Value</th><th>Source</th><th>Comment</th></tr>
<tr><td colspan="4">Treatment utilisation (year 0= 2025)</td></tr>
<tr><td>Venetoclax initiating scripts (projected current market)</td><td>
<table>
<tr><th>Yr</th><th>Total V (VO/IV) initial scripts</th><th>VO share (%)</th><th>V (VO) initial scripts</th><th>IV share (%)</th><th>V (IV) initial scripts</th></tr>
<tr><td>Y0</td><td>522</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>Y1</td><td>531</td><td>70%</td><td>372</td><td>30%</td><td>159</td></tr>
<tr><td>Y2</td><td>540</td><td>60%</td><td>324</td><td>40%</td><td>216</td></tr>
<tr><td>Y3</td><td>549</td><td>50%</td><td>275</td><td>50%</td><td>275</td></tr>
<tr><td>Y4</td><td>558</td><td>40%</td><td>223</td><td>60%</td><td>335</td></tr>
<tr><td>Y5</td><td>568</td><td>40%</td><td>227</td><td>60%</td><td>341</td></tr>
<tr><td>Y6</td><td>578</td><td>40%</td><td>231</td><td>60%</td><td>347</td></tr>
</table>
</td><td>2025 V (VO/IV) scripts: PBS/ RPBS (Jun 2024–May 2025). Growth (2026–2031): 1.7% = population growth (ABS 2024). Market shares: para 6.89, ibrutinib PSD, PBAC Mar 2024.</td><td>V (VO/IV) market growth projections (i.e., +1.7%/year) may be overestimated, particularly considering shifts in utilisation to TTP regimens (para 6.89, ibrutinib PSD, March 2024 PBAC meeting). Additionally, the estimated uptake rate of IV from VO (in the absence of AV) may be overstated given alternative 1L CLL/SLL options, particularly zanubrutinib.</td></tr>
<tr><td>Total scripts (projected current market)</td><td>
<table>
<tr><th>Yr</th><th>Total * V (VO) scripts</th><th>O (VO) scripts (public)</th><th>O (VO) scripts (private)</th><th>Total * V (IV) scripts</th><th>I (IV) scripts</th></tr>
<tr><td>Calc</td><td>Initial V (VO) × 9.67</td><td>Initial V (VO)×7.355 × 34%</td><td>Initial V (VO)×7.355 × 66%</td><td>Initial V (IV) ×10.43</td><td>Initial V (IV) × 12.06</td></tr>
<tr><td>Y1</td><td>3593</td><td>917</td><td>1816</td><td>1661</td><td>1921</td></tr>
<tr><td>Y2</td><td>3132</td><td>800</td><td>1583</td><td>2252</td><td>2604</td></tr>
<tr><td>Y3</td><td>2655</td><td>678</td><td>1342</td><td>2863</td><td>3311</td></tr>
<tr><td>Y4</td><td>2160</td><td>551</td><td>1092</td><td>3495</td><td>4041</td></tr>
<tr><td>Y5</td><td>2197</td><td>561</td><td>1110</td><td>3554</td><td>4109</td></tr>
<tr><td>Y6</td><td>2234</td><td>570</td><td>1129</td><td>3614</td><td>4179</td></tr>
</table>
* Total: initiating + continuing scripts
</td><td>The estimate was derived by multiplying the number of V (VO/IV) initiation scripts by the equi-effective doses. O (VO) scripts were also estimated using the public/private hospital share.</td><td>The number of scripts was consistent with previous PBAC decisions (para 7.12, ibrutinib PSD, March 2024 PBAC meeting) and with Section 3 of the current submission.</td></tr>
<tr><td colspan="4">Expected market</td></tr>
<tr><td>Displacement of IV & VO by AV</td><td>
<table>
<tr><th>Yr</th><th>AV uptake from VO (%)</th><th>AV uptake from IV (%)</th><th>AV share (%)</th><th>VO share (%)</th><th>IV share (%)</th></tr>
<tr><td>Y0</td><td>NA</td><td>NA</td><td>0%</td><td>75%</td><td>25%</td></tr>
<tr><td>Y1</td><td colspan="5" rowspan="6">[redacted]</td></tr>
<tr><td>Y2</td></tr>
<tr><td>Y3</td></tr>
<tr><td>Y4</td></tr>
<tr><td>Y5</td></tr>
<tr><td>Y6</td></tr>
</table>
</td><td>Sponsor's estimation of displacement</td><td>The ESC considered the proposed uptake rates of AV to be too high and that it was more likely that VO would maintain a [redacted]% market share by year 6.</td></tr>
<tr><td>Substitution rates</td><td>
<table>
<tr><th>A (AV) subst. V (IV)</th><th>V (IV)</th><th>A (AV)</th><th>Subst. rate</th></tr>
<tr><td>Venetoclax Initial</td><td>1</td><td>2</td><td>2.00</td></tr>
<tr><td>Venetoclax 1st continuing</td><td>5</td><td>5</td><td>1.00</td></tr>
<tr><td>Venetoclax 2nd continuing</td><td>4.43</td><td>5.97</td><td>1.35</td></tr>
<tr><th>V (AV) subst. I (IV)</th><th>I (IV)</th><th>V (AV)</th><th>Subst. rate</th></tr>
<tr><td>Initial</td><td>3</td><td>1.00</td><td>0.33</td></tr>
<tr><td>1st continuing</td><td>6</td><td>5.00</td><td>0.83</td></tr>
<tr><td>2nd continuing</td><td>3.06</td><td>4.84</td><td>1.58</td></tr>
<tr><td>Total</td><td>12.06</td><td>10.84</td><td>0.90</td></tr>
<tr><th>A (AV) subst. V (VO)</th><th>V (VO)</th><th>A (AV)</th><th>Subst. rate</th></tr>
<tr><td>Venetoclax Initial</td><td>1</td><td>2</td><td>2.00</td></tr>
<tr><td>Venetoclax 1st continuing</td><td>5</td><td>5</td><td>1.00</td></tr>
<tr><td>Venetoclax 2nd continuing</td><td>3.67</td><td>5.97</td><td>1.63</td></tr>
<tr><th>V (AV) subst. O (VO)</th><th>O (VO)</th><th>V (AV)</th><th>Subst. rate</th></tr>
<tr><td>Obinutuzumab</td><td>7.36</td><td>10.84</td><td>1.47</td></tr>
</table>
</td><td>The equi-effective doses for VO and IV: Para 6.78, ibrutinib PSD, March 2024 PBAC meeting. The equi-effective doses for AV: estimated by the submission.</td><td>Substitution rates were correctly calculated.</td></tr>
<tr><td colspan="4">Costs</td></tr>
</table>

Data	Value					Source	Comment
Proposed regimen (effective prices)	**Drug**	**Index**	**Max Q**	**AEMP ($)**	**DPMQ ($)**	Proposed by the sponsor,	Consistent with Section 3 of the submission. Using this, the total treatment cost of AV was $[redacted].
	A (AV)	All	56	[redacted]	[redacted]		
	V (AV)	Initial	1				
	V (AV)	Continuing	1				
PBS/RPBS split	PBS: 97.20%, RPBS: 2.80%					Estimated from V (VO), O (VO), I (IV), & V (IV) markets (initial, continuing, GF) in PBS (Jun24-May25).	This was reasonable.
Average co-pay	PBS: $16.18, RPBS: $5.71						
Comparator (effective prices)	**Drug**	**Index**	**Max Q**	**AEMP ($)**	**DPMQ ($)**	PBS item codes [a]	Consistent with the estimated effective AEMPs in Section 3 of the submission. Using these, the total treatment cost of VO and IV regimens was $[redacted] and $[redacted], respectively.
	V (VO)	Initial	28	[redacted]	[redacted]		
		Continuing	28				
	O (VO)	Public hospital	1	$4,525.52	$4,616.75		
		Private hospital	1		$4,725.78		
	V (IV)	Initial	28	[redacted]	[redacted]		
	V (IV)	Continuing	28				
	I (IV)	All	30				
MBS costs	Intravenous administration for O (VO): Parenteral administration, MBS item 13950= $126.00 Professional attendance, MBS item 116= $89.40. MBS costs of I (IV) regarding AF monitoring, were excluded.					MBS item codes	MBS item 116 should be excluded from the calculation for savings in MBS.

Source: Compiled during the evaluation from Table 4-1, pp137-138, Table 4-2, p140, Tables 4-3 and 4-4, p143, Table 4-5, p144, Table 4-6 and 4-7, p146, Table 4-7, p147, Tables 4-9 and 4-10, p148, Tables 4-11 and 4-12, p149, Table 4-16, p153, Tables 4-17 and 4-18, p154, Table 4-19, p155, and Table 4-21, p157 of the submission.

A=acalabrutinib; AV=acalabrutinib+venetoclax; CLL=chronic lymphocytic leukaemia; cont=continuing; FD=fixed duration; GF=grandfather; I=ibrutinib; IV=ibrutinib+venetoclax; MBS=Medicare Benefits Schedule; O=obinutuzumab; PBS=Pharmaceutical Benefits Scheme; PSD=Product Specific Document; Q=quantity; RPBS=Repatriation Pharmaceutical Benefits Scheme; TTP=treat to progression; V=venetoclax; VO=venetoclax+obinutuzumab.

Note: X (XZ) refers to treatment X as part of the XZ regimen.

[a] PBS item codes: V (VO): 12188L (initial), 2205J (1st continuing), 2199C (2nd continuing), O (VO): 12204H (public hospital), 12193R (private hospital); V (IV): 14584N (initial), 14585P (1st continuing), 14595E (2nd continuing), I (IV): 14597G, 14580J, 14598H (initial) 14604P, 14620L, 14603N (1st continuing) 14596F, 14621M (2nd continuing).

6.41 The ESC considered the proposed uptake rate of AV to be overestimated given the lack of added benefit for most patients, noting AV has non-inferior efficacy and a potentially favourable safety profile compared to OV. The ESC advised that in clinical practice clinicians will be somewhat reluctant to use two effective therapies up front that will mean there are no effective treatment options when patients relapse, and it considered it was more likely that VO, as the current market leader in first-line, would maintain about a [redacted]% market share by Year 6. Acalabrutinib as a second generation BTKi is generally better tolerated as compared to ibrutinib. As such, the ESC expected that AV, as an all-oral therapy and with fewer side effects than ibrutinib, would dominate IV for the remainder of the market ([redacted]% to [redacted]%).

6.42 Table 11 presents the estimated utilisation and financial implications (using the estimated effective DPMQ) of the PBS listing of AV for the first-line treatment of CLL/SLL.

Table 11: Estimated use and financial implications

	2026	2027	2028	2029	2030	2031	Total
Estimated extent of use of the proposed medicine (AV)							
Number of A (AV) scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Number of V (AV) scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Total AV scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4]
Cost to PBS/RPBS of the proposed medicine (AV), (less co-payments)							
Costs of A (AV) ($)	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][7]
Costs of V (AV) ($)	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][8]
Total costs of AV ($)	[redacted][6]	[redacted][6]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][10]
Estimated change in use of other medicines (IV, VO)							
Number of V (VO) scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][3]
Number of O (VO) scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of I (IV) scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][11]
Number of V (IV) scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][11]
Cost to PBS/RPBS of other medicines (IV, VO) (less co-payments)							
Cost-offsets (VO) (-$)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][121]
Cost-offsets (IV) (-$)	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][13]
Total cost-offsets (-$)	[redacted][6]	[redacted][6]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][10]
Net cost, PBS/RPBS ($)	[redacted][5]	[redacted][5]	[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]
Cost to MBS							
Administration of O (VO) (-$)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Consultations for O (VO) (-$)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net cost to MBS (-$)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net financial implications							
Net cost, PBS/RPBS/MBS ($)	[redacted][5]	[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]

Source: Table 4-12, p149, Table 4-15, p152, Table 4-16, p153, Table 4-17, p154, Table 4-18, p154, Table 4-19, p155, Table 4-23, p159, Table 4-25, p161, Table 4-27, p163, Table 4-29, p164, Table 4-31, p165, and Table 4-33, p166 of the submission.
A=acalabrutinib; AV=acalabrutinib+venetoclax; I=ibrutinib; IV=ibrutinib+venetoclax; MBS=Medicare Benefits Schedule; O=obinutuzumab; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme; V=venetoclax; VO=venetoclax+obinutuzumab.
The redacted values correspond to the following values:
[1] *500 to < 5,000*
[2] *20,000 to < 30,000*
[3] *5,000 to < 10,000*
[4] *40,000 to < 50,000*
[5] *$0 to < $10 million*
[6] *$10 million to < $20 million*
[7] *$60 million to < $70 million*
[8] *$70 million to <$80 million*
[9] *$20 million to < $30 million*
[10] *$100 million to < $200 million*
[11] *10,000 to < 20,000*
[12] *$40 million to < $50 million*
[13] *$90 million to < $100 million*

6.43 The net cost to the PBS/RPBS was $0 to < $10 million in Year 1, decreasing to $0 to < -$10 million in Year 6, resulting in a cumulative net saving of $0 to < $10 million over the first six years of listing AV in untreated CLL/SLL. The estimated net cost savings to the PBS/RPBS were due to the assumed relative change in market shares between VO and IV (VO is less costly to the PBS than IV and would gain a relatively higher market share compared to IV) rather than the direct substitution with AV (AV has slightly higher drug-related treatment costs than VO and IV, due to administration of infusions for VO and difference in number of venetoclax script for IV).

6.44 Overall, the estimated number of AV scripts presented in the submission was likely an overestimate due to the high uptake assumptions; but given AV is anticipated to substitute for treatments with a similar cost per patient, the net effect of the proposed listing is expected to be approximately cost neutral, irrespective of the absolute number of scripts.

Financial Management – Risk Sharing Arrangements (RSA)

6.45 The submission noted that, given uncertainty in the uptake rate of AV and the overall FD regimen market dynamics, the sponsor may be open to considering a RSA; however, any such arrangement would need to appropriately account for the potential use of acalabrutinib and align with the overall FD regimen market context.

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

7 PBAC Outcome

7.1 The PBAC deferred making its decision on whether to recommend the Authority Required listing of acalabrutinib for use in combination with venetoclax (AV) in a fixed duration (FD) regimen for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), noting that a TGA Delegate's Overview was not available at the time of the PBAC meeting. The PBAC was of a mind to recommend AV and considered amongst other matters, that AV would be acceptably cost-effective if it was cost-minimised to venetoclax given in combination with obinutuzumab (VO).

7.2 The PBAC noted that, while multiple treatment options are available, there was a moderate clinical need for a second all oral, FD treatment option which would increase access for rural and regional patients and reduce the burden of treatment, compared to VO, which involves intravenous infusion. AV would also provide an effective treatment option that is likely better tolerated by some patients than VO or ibrutinib with venetoclax (IV), the currently available oral FD regimen.

7.3 The PBAC considered that the current alternative FD treatments, IV and VO, were the appropriate comparators.

7.4 The PBAC noted the submission's claim that AV is non-inferior in comparative effectiveness to IV and VO was based on indirect clinical evidence from 6 trials/studies investigating the efficacy and safety of AV (AMPLIFY) compared to VO (CLL13, CRISTALLO, CLL14), or IV (GLOW, CAPTIVATE). The PBAC noted the main analysis presented in the submission was an anchored (Bucher) indirect treatment comparison (ITC) that showed no statistically significant difference between AV and VO with respect to progression free survival (PFS) and overall survival (OS) (see Table 4). Additionally, the PBAC noted that supportive evidence from unanchored ITCs (Figure 2) and simulated treatment comparisons (Table 5) showed no significant difference between AV and VO or AV and IV.

7.5 The PBAC noted that the submission had not presented results from AMPLIFY for the

key secondary endpoint of minimal residual disease negativity rate (undetectable minimal residual disease (uMRD)), which the Committee noted is recognised as clinically meaningful in trials and generally accepted as predictive of PFS. The Committee noted that in AMPLIFY, the MRD negativity rate was lower in patients treated with AV rather than immunochemotherapy, and that the percentage of patients with peripheral blood (PB) uMRD (<1 CLL cell per 10,000 leukocytes) was 26.8% in the AV group and 51% in the FCR/BR group at cycle 9 day 1 (TGA 2nd Round Clinical Evaluation Report), 34.4% versus 45.5% at the end of treatment, and 29.9% versus 51% at 3 months post-treatment[1]. In comparison, the PBAC noted that PB uMRD $<10^{-4}$ was 54.7% at the end of treatment plus 3 months for patients treated with IV in GLOW, and 77% at end of treatment plus 1 month for patients treated with IV in CAPTIVATE[1]. The PBAC considered that these results introduced some uncertainty regarding the submission's claim that AV is non-inferior in terms of comparative effectiveness to IV.

7.6 Overall, the PBAC considered that the claim of non-inferior comparative effectiveness to IV and to VO was likely reasonable, with some uncertainty due to uMRD rates.

7.7 The PBAC noted that based on unanchored ITCs, fewer Grade ≥3 adverse events (severe infection, neutropenia, infusion reactions and tumour lysis syndrome) were reported for patients treated with AV compared to VO, and fewer Grade ≥3 adverse events (atrial fibrillation, hypertension) were reported for patients treated with AV compared to IV. The PBAC considered that while the claims of superior comparative safety to IV and a more favourable safety profile compared to VO were difficult to assess based on the evidence presented, the claims were likely reasonable.

7.8 The PBAC noted the submission presented a cost-minimisation approach comparing AV to VO, which it considered was appropriate, as the VO comparison provided the main clinical analysis and was the most established FD treatment regimen. The PBAC considered the equi-effective doses to be 12.97 acalabrutinib scripts and 10.84 venetoclax scripts are equivalent to one initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts. The PBAC accepted the other costs and cost offsets related to TLS and administration were appropriate.

7.9 The PBAC noted the submission had used a market share approach to estimate the financial implications of listing AV on the PBS, which assumed that AV would only substitute for other FD regimens (VO and IV). The PBAC considered this assumption was poorly justified and that AV was also likely to take market share from acalabrutinib plus or minus obinutuzumab and from zanubrutinib, which were used as treat to progression therapies. The PBAC considered the treatment uptake rate for AV was likely overestimated and that the estimates of uptake as outlined in paragraph 6.41

[1] Tedeschi, A., Frustaci, A.M., Menna, P. *et al.* Fixed-duration therapy of chronic lymphocytic leukemia with venetoclax and Bruton tyrosine kinase inhibitors: an insight into differences between ibrutinib and acalabrutinib. *Leukemia* **39**, 2618–2621 (2025). https://doi.org/10.1038/s41375-025-02778-1

(based on the ESC consideration) were more reasonable, particularly given reported differences in uMRD rates. Additionally, the PBAC considered that the professional attendance fee (MBS item 116) should be excluded from the calculation of MBS savings given AV patients will likely require frequent specialist visits in early treatment phases. The PBAC considered that given AV is anticipated to substitute for treatments with a similar cost per patients, the net effect of the proposed listing is expected to be approximately cost neutral.

7.10 The PBAC noted that Risk Sharing Arrangements (RSAs) consisting of subsidisation caps are in place for both ibrutinib and for venetoclax for the treatment of patients with previously untreated CLL/SLL. The PBAC considered it would be reasonable for AV to join the existing RSA for IV, given AV was expected to take majority of that market, due to increased risk of atrial fibrillation, or hypertension events with IV. The PBAC considered that as AV is expected to replace both VO and IV, an increase in the use of venetoclax or ibrutinib is not expected, and therefore no increase in the financial caps would be required to account for the new listing.

7.11 The PBAC will make a decision on whether to recommend AV in a FD regimen for the treatment of previously untreated CLL or SLL based on receipt of the TGA Delegate's Overview.

Outcome:
Deferred

Addendum to the November 2025 PBAC Public Summary Document:

ACALABRUTINIB,
Tablet,
100 mg,
Calquence®,
ASTRAZENECA PTY LTD.

8 Purpose

8.1 For the PBAC to consider whether to recommend listing acalabrutinib for use in combination with venetoclax (AV) in a fixed duration (FD) regimen for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic

lymphoma (SLL), given that a positive TGA Delegate's Overview was now available.

9 Background

9.1 At its meeting between 5 – 7 November 2025, the PBAC deferred making a decision on whether to recommend listing acalabrutinib for use in combination with venetoclax (AV) in a fixed duration (FD) regimen for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), noting that a TGA Delegate's Overview was not available at the time of the PBAC meeting.

10 Current situation

10.1 On 12 November 2025, the TGA Delegate's Overview was received. The TGA Delegate stated, "I am currently inclined to approve the proposed extension of indication for acalabrutinib to include first-line treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) in combination with venetoclax (AV)".

11 PBAC Outcome

11.1 The PBAC recommended extending the PBS listing of acalabrutinib to include use in combination with venetoclax in a FD regimen for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The PBAC recalled that at its meeting between 5 – 7 November it had been of a mind to make a recommendation but was not able to do so given a TGA Delegate's Overview was not available. The PBAC noted that the TGA Delegate's Overview for acalabrutinib had been received and that the Delegate was inclined to approve the proposed extension of indication for acalabrutinib. The PBAC reaffirmed its view that amongst other matters, AV would be acceptably cost-effective if it was cost-minimised to venetoclax given in combination with obinutuzumab (VO) with the equi-effective doses being: 12.97 acalabrutinib scripts and 10.84 venetoclax scripts are equivalent to one initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts, and that acalabrutinib and venetoclax should join the Risk Sharing Arrangements that are in place for both ibrutinib and for venetoclax for the treatment of patients with previously untreated CLL/SLL.

11.2 The PBAC considered that consistent with existing acalabrutinib listings, an Authority Required telephone/electronic (via online PBS Authorities) listing for both the initial/grandfathering and continuing treatment phases would be appropriate.

11.3 The PBAC noted that the submission requested a grandfather restriction for acalabrutinib. The submission did not, however, mention when the early access program would initiate and whether patients on treatment with AV via an early access program from cycle 3 onwards would also need to be able to transition to PBS-subsidised treatment. Furthermore, a grandfather restriction for venetoclax was not presented in the submission. The PBAC also noted that there may need to be grandfather restrictions for venetoclax, to allow non-PBS subsidised patients receiving

AV to transition to PBS-subsidised treatment.

11.4 The PBAC noted that flow-on changes would be required to create a new restriction for venetoclax to allow for its use in conjunction with acalabrutinib.

11.5 The PBAC considered that flow-on changes to add the clinical criteria "The treatment must not be in combination with acalabrutinib" to the venetoclax listings (PBS item codes: 12193R; 12204H; 12205J; 12188L; 12199C) and to add the clinical criteria "The treatment must not be in combination with venetoclax" to the existing obinutuzumab listings (PBS item codes: 13787P; 13793Y; 13810W), would be required to prevent acalabrutinib and venetoclax being used as part of triple therapy with obinutuzumab.

11.6 The PBAC recalled that it had made a recommendation at its July 2025 PBAC meeting to add nurse practitioners to the eligible prescriber types for the Bruton's tyrosine kinase inhibitors (BTKi) as part of the nurse practitioners/endorsed midwives prescribing review. For various oncology and haematology medicines and indications, the PBAC considered that nurse practitioner prescribing is suitable to continue therapy provided that patient care is shared with a medical practitioner. The PBAC recommended that the July 2025 nurse practitioner recommendation for the BTKi medicines also be applied to the new acalabrutinib listing, but that the timing of the addition of nurse practitioners to this new acalabrutinib listing would depend on whether the listing proceeds before, at the same time or after the broader July 2025 PBAC nurse practitioner recommendations are implemented. In July 2025, the PBAC did not recommend adding nurse practitioners as an eligible prescriber type for venetoclax, citing the medicine specific considerations (general guidance principle 3 on prescriber type determination) of difficult dose titration with a high risk of toxicity as the reason for excluding venetoclax.

11.7 Acalabrutinib should not be exempt from the Early Supply Rule as it currently applies to similar drugs including venetoclax for previously untreated CLL/SLL.

11.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because AV is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over VO, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines - Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

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

12 Recommended listing

12.1 Add new items as follows:

Initial treatment (Cycles 1-2)

Category / Program: ☒ GENERAL - General Schedule (Code GE)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	NEW 1 MP	1	56	1	Calquence
Restriction Summary [new1] / Treatment of Concept [new1]: Authority Required					
Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.					
Administrative Advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy - see 'Indications for treatment' section; and (2) recognising progressive disease - see 'Definition of response, relapse, and refractory disease' section. See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Initial treatment (treatment cycles 1 to 2 inclusive) in first-line therapy					
Clinical criteria:					
The condition must be untreated with drug treatment at the time of the first dose of this drug; or					
Patient must have developed an intolerance of a severity necessitating permanent treatment withdrawal following use of another drug PBS indicated as first-line drug treatment of CLL/SLL					
AND					
Clinical criteria:					
The treatment must only be prescribed for a patient with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition					
AND					
Clinical criteria:					
The treatment must be initiated as monotherapy, with the intention of use in combination with venetoclax from cycle 3 to 14					
AND					
Clinical criteria:					
The treatment must not be in combination with obinutuzumab					

Continuing treatment (Cycles 3- 14)

Category / Program: ☒ GENERAL - General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	NEW 2 MP NP	1	56	5	Calquence
Restriction Summary [new2] / Treatment of Concept [new2]: Authority Required					

Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: Continuing treatment (treatment cycles 3 to 14 inclusive) of first-line therapy – in combination with venetoclax
Clinical criteria:
Patient must have previously received monotherapy with this drug as their most recent course of PBS-subsidised treatment for this condition
AND
Clinical criteria:
The treatment must not exceed 14 cycles in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first.
AND
Clinical criteria:
The treatment must be in combination with venetoclax
AND
Clinical criteria:
The treatment must not be in combination with obinutuzumab
Treatment criteria:
Must be treated by a medical practitioner; or
Must be treated by a nurse practitioner where both of the following are occurring: (i) patient care is being shared with a medical practitioner, (ii) the prescription continues existing therapy with this medicine.

Grandfather treatment

Category / Program: ☒ GENERAL - General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	NEW 3 MP	1	56	5	Calquence
Restriction Summary [new3] / Treatment of Concept [new3]: Authority Required					
Administrative Advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy - see 'Indications for treatment' section; and (2) recognising progressive disease - see 'Definition of response, relapse, and refractory disease' section. See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					

Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply in first-line therapy – Grandfather arrangements
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date XXX]
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition
AND
Clinical criteria:
The condition must have been untreated with drug treatment at the time of the first dose of this drug;
OR
Patient must have developed an intolerance of a severity necessitating permanent treatment withdrawal following use of another drug PBS indicated as first-line treatment of CLL/SLL prior to initiating non-PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
The treatment must only be prescribed for a patient with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition
AND
Clinical criteria:
The treatment must be in combination with venetoclax as continuing treatment for this condition (treatment cycles 3 to 14 inclusive);
OR
The treatment must be as monotherapy for initial treatment of this condition (treatment cycles 1 to 2 inclusive)
AND
Clinical criteria:
The treatment must not be in combination with obinutuzumab
AND
Clinical criteria:
The treatment must not exceed 14 cycles in total with this drug, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first
Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only.
Prescribing Instructions: For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the next relevant treatment phase.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

12.2 Flow-ons to add new venetoclax listings:

Initial treatment (Cycle 3)

Category / Program: ☒ GENERAL - General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
VENETOCLAX					

venetoclax 10 mg tablet [14] (&) venetoclax 50 mg tablet [7] (&) venetoclax 100 mg tablet [7] (&) venetoclax 100 mg tablet [14], 1 pack	NEW 4 MP	1	1	0	Venclexta
Restriction Summary [new4] / Treatment of Concept [new4]: Authority Required					
Administrative Advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy - see 'Indications for treatment' section; and (2) recognising progressive disease - see 'Definition of response, relapse, and refractory disease' section. See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.					
Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Initial treatment in first-line therapy with acalabrutinib - Dose titration (cycle 3)					
Clinical criteria:					
The condition must be untreated with venetoclax at the time of the first dose of this drug; or					
Patient must have developed an intolerance of a severity necessitating permanent treatment withdrawal following use of another drug PBS indicated as first-line drug treatment of CLL/SLL					
AND					
Clinical criteria:					
The treatment must only be prescribed for a patient with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition					
AND					
Clinical criteria:					
The treatment must be in combination with acalabrutinib					
AND					
Clinical criteria:					
The treatment must not be in combination with obinutuzumab					

First continuing treatment (Cycle 4-8)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
venetoclax 100 mg tablet, 120	NEW 5 MP	1	120	4	Venclexta
Restriction Summary [new5] / Treatment of Concept: [new5] Authority required					

Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: First continuing treatment (treatment cycles 4 to 8 inclusive) of first-line therapy with acalabrutinib
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be in combination with acalabrutinib
AND
Clinical criteria:
The treatment must not be in combination with obinutuzumab
AND
Clinical criteria:
The treatment must cease upon disease progression

Second and final continuing treatment (Cycle 9-14)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
venetoclax 100 mg tablet, 120	NEW 6 MP	1	120	5	Venclexta
Restriction Summary [new6] / Treatment of Concept: [new6] Authority required					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Second and final continuing treatment (treatment cycles 9 to 14 inclusive) of first-line therapy with acalabrutinib					
Clinical criteria:					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria:					
The treatment must be in combination with acalabrutinib					
AND					
Clinical criteria:					
The treatment must not be in combination with obinutuzumab					
AND					
Clinical criteria:					
The treatment must not exceed 12 cycles in total with this drug, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first.					

12.3 Flow-on changes to existing venetoclax and obinutuzumab listings:

Flow-ons to existing venetoclax listings

To prevent triple therapy with acalabrutinib, add the following clinical criteria to the venetoclax listings in combination with obinutuzumab (PBS item codes: 12193R; 12204H; 12205J; 12188L; 12199C).

Clinical Criteria: The treatment must not be in combination with acalabrutinib.

Flow-ons to existing obinutuzumab listings

To prevent triple therapy with venetoclax, add the following clinical criteria to the obinutuzumab listings in combination with acalabrutinib (PBS item codes: 13787P; 13793Y; 13810W)

Clinical Criteria:
The treatment must not be in combination with venetoclax.

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

13 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.

14 Sponsor's Comment

The sponsor had no comment.