

7.01 ACALABRUTINIB, Tablet 100 mg, Calquence[®], AstraZeneca Pty Ltd

1 Purpose of resubmission

- 1.1 The standard re-entry submission requested Authority Required, listing for acalabrutinib (ACA) as monotherapy or in combination with obinutuzumab (OBIN) for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).
- 1.2 Listing was requested based on a cost-minimisation approach (CMA) versus venetoclax in combination with obinutuzumab (VTX+OBIN).

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

Component	Description
Population	Patients with previously untreated CLL/SLL.
Intervention	Acalabrutinib 100 mg tablet twice a day monotherapy (ACA) or acalabrutinib 100 mg tablet twice a day in conjunction with obinutuzumab (ACA+OBIN).
Comparator	Venetoclax plus obinutuzumab (VTX+OBIN).
Outcomes	Progression-free survival (PFS), overall response rate (ORR), overall survival (OS), and safety.
Clinical claim	In patients with previously untreated CLL, ACA+/-OBIN is non-inferior to VTX+OBIN in terms of overall efficacy and superior to VTX+OBIN in terms of safety.

Source: Table 1.2, p. 43 of the resubmission

ACA = acalabrutinib, CLL = chronic lymphocytic leukaemia, OBIN = obinutuzumab, ORR= overall response rate, OS= overall survival, PFS= progression-free survival, SLL = small lymphocytic lymphoma, VTX= venetoclax

2 Background

Registration status

- 2.1 Acalabrutinib 100 mg capsules were approved in November 2019 by the TGA for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy, and for the treatment of patients with CLL/SLL.
- 2.2 The tablet formulation of ACA was included on the Australian Register of Therapeutic Goods (ARTG) in October 2022. The tablet formulation of ACA was approved for the same indications that apply to the original capsule formulation, with ACA 100 mg capsule and ACA 100 mg tablet considered bioequivalent.

Previous PBAC consideration

- 2.3 This resubmission was the fourth submission for ACA as monotherapy or in combination with OBIN for the treatment of patients with previously untreated CLL/SLL.

- 2.4 Previous submissions were considered by the PBAC for untreated CLL/SLL at the July 2020 (ACA+/-OBIN), November 2021 (ACA monotherapy) and December 2022 intracycle (ACA+OBIN) PBAC meetings.
- 2.5 At the most recent PBAC consideration, ACA+OBIN was considered for untreated CLL/SLL patients who are considered unsuitable for treatment with fludarabine-based chemoimmunotherapy but was not recommended. At its December 2022 meeting (paragraph 7.1, ACA, Public Summary Document (PSD), December 2022 PBAC intracycle meeting), the PBAC considered that:
- The claim of superior effectiveness or safety of ACA+OBIN vs VTX+OBIN was not supported by the evidence due to differences in patient populations between the trials which did not appear to be adequately accounted for in the matching adjusted indirect comparison (MAIC).
 - A claim of non-inferiority would be more appropriate.
 - A cost-minimisation approach would be more appropriate, rather than the cost utility analysis submitted.
 - A substantial price reduction would be required for ACA+OBIN to be considered acceptably cost-effective.
- 2.6 The PBAC also advised that the criterion that patients be ‘inappropriate for fludarabine-based chemoimmunotherapy’ should be removed from the existing VTX+OBIN restriction. It would appear appropriate not to include this criterion for ACA+/-OBIN (paragraph 7.3, ACA, PSD, December 2022 PBAC intracycle meeting).
- 2.7 Table 2 summarises the key matters of concern from the previous PBAC considerations and how the resubmission addressed these.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addressed it
Clinical place in therapy	<ul style="list-style-type: none"> The PBAC considered that ACA monotherapy would be used in most patients unsuitable for treatment with a purine analogue given the additional toxicity of combination therapy together with the general frailty of the patient population (paragraph 7.3, ACA, PSD, July 2020 PBAC meeting). The PBAC, at its December 2022 intracycle meeting, considered that it would be clinically appropriate to enable access to ACA monotherapy given it may be preferred by some patients due to lower toxicity compared to ACA+OBIN and given it is an oral treatment that does not require hospitalisation (paragraph 7.5, ACA, PSD, December 2022 PBAC intracycle meeting). 	<p>Addressed.</p> <ul style="list-style-type: none"> Listing was requested for ACA monotherapy and ACA+OBIN.
	<ul style="list-style-type: none"> The PBAC considered that the existing VTX+OBIN restriction for first-line CLL/SLL should remove the criterion that patients be 'inappropriate for fludarabine-based chemoimmunotherapy'. This criterion should also not be included for ACA+OBIN (paragraph 7.3, ACA, PSD, December 2022 PBAC intracycle meeting). 	<p>Addressed.</p> <ul style="list-style-type: none"> The resubmission proposed to remove the criterion 'inappropriate for fludarabine-based chemoimmunotherapy' from the restriction, based on PBAC advice.
Clinical effectiveness	<ul style="list-style-type: none"> The claim of superior effectiveness or safety of ACA+OBIN vs VTX+OBIN was not supported due to differences in patient populations between the trials which did not appear to be adequately accounted for in the MAIC (paragraph 7.1, ACA, PSD, December 2022 PBAC intracycle meeting). A claim of non-inferiority would be more appropriate (paragraph 7.9, ACA, PSD, December 2022 PBAC intracycle meeting). 	<p>The resubmission made a claim of non-inferiority for effectiveness and superiority for safety. The pre-PBAC response stated the sponsor pragmatically accepted a clinical claim of non-inferiority.</p> <p>For the MAIC:</p> <ul style="list-style-type: none"> Baseline characteristics before and after matching were not available. The resubmission did not address the request made by the PBAC that the MAIC should adjust for all effect modifiers and prognostic variables to predict outcomes reliably.
Economic evaluation	<ul style="list-style-type: none"> The PBAC suggested that "a cost-minimisation approach would be more appropriate, rather than the cost utility analysis submitted" (paragraph 7.12, ACA, PSD, December 2022 PBAC intracycle meeting) based on the clinical evidence. 	<p>Addressed.</p> <ul style="list-style-type: none"> A CMA was presented in the resubmission.

Source: Table 1.5, pp.51-53 of the resubmission and Table 2, pp.3-5 of the PBAC PSD, December 2022 PBAC intracycle meeting
 ACA= acalabrutinib, CMA = cost minimisation approach, MAIC = matching adjusted indirect comparison, OBIN = obinutuzumab, PSD = public summary document, VTX= venetoclax

3 Requested listing

3.1 The requested restriction is below. Changes to the restriction versus that considered at the December 2022 intracycle PBAC meeting are noted with strikethrough.

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Medicinal product pack	Dispensed Price for Maximum Quantity (DPMQ)	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ACALABRUTINIB					
Acalabrutinib 100 mg tablet, 56	\$8,219.02 published price TBD effective price	1	56	6 (initial) 5 (continuing)	Calquence®

Source: Table 1.7, p.59 of the resubmission.

Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Patients with untreated CLL/SLL
Treatment Phase: Initial
Clinical criteria:
The condition must be previously untreated
AND
Clinical criteria:
Patient must be considered unsuitable for fludarabine-based chemoimmunotherapy
AND
Clinical criteria:
Patient must have creatinine clearance (CrCl) ≥ 30 mL/min
AND
Clinical criteria:
Patient must have Cumulative Illness Rating Scale score of >6 (excluding CLL-induced illness or organ damage) OR patient must have a CrCl <70 mL/min
AND
Clinical criteria:
The treatment must be as monotherapy

Source: Table 1.8, pp.59-60 of the resubmission.

Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Patients with untreated CLL/SLL
Treatment Phase: Initial
Clinical criteria:
The condition must be previously untreated
AND
Clinical criteria:
Patient must be considered unsuitable for fludarabine-based chemoimmunotherapy
AND
Clinical criteria:
Acalabrutinib must be initiated as a monotherapy for 1 Cycle with treatment in combination with obinutuzumab commencing in Cycle 2 Day 1
AND
Clinical criteria:
Patient must have creatinine clearance (CrCl) ≥ 30 mL/min
AND
Clinical criteria:

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~~Patient must have Cumulative Illness Rating Scale score of >6 (excluding CLL-induced illness or organ damage) OR patient must have a CrCl <70 mL/min~~

Source: Table 1.9, p.60 of the resubmission

Restriction type: <input checked="" type="checkbox"/> Streamlined
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Patients with untreated CLL/SLL
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be as monotherapy

Source: Table 1.10, p.62 of the resubmission

Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Patients with untreated CLL/SLL
Treatment Phase: Initial
Clinical criteria:
Patient must have previously received non-PBS-subsidised treatment with this drug for previously untreated CLL/SLL prior to [PBS-listing date of acalabrutinib]
AND
Clinical criteria:
Patient must have creatinine clearance (CrCl) ≥ 30 mL/min
AND
Clinical criteria:
The treatment must be as monotherapy

Source: Table 1.11, pp.62-63 of the resubmission.

Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Patients with untreated CLL/SLL
Treatment Phase: Initial
Clinical criteria:
Patient must have previously received non-PBS-subsidised treatment with this drug for previously untreated CLL/SLL prior to [PBS-listing date of acalabrutinib]
AND
Clinical criteria:
ACA monotherapy must be initiated for 1 Cycle with treatment in combination with obinutuzumab commencing in Cycle 2 Day 1
AND
Clinical criteria:
Patient must have creatinine clearance (CrCl) ≥ 30 mL/min

Source: Table 1.12, pp.63-64 of the resubmission.

Restriction type: <input checked="" type="checkbox"/> Streamlined
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Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Patients with untreated CLL/SLL
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be as monotherapy

Source: Table 1.13, p.64 of the resubmission.

- 3.2 It was noted that the resubmission requested grandfathering for both initial and continuing treatment criteria.

4 Population and disease

- 4.1 CLL is an indolent malignant disorder of white blood cells, characterised by increased production of mature but dysfunctional B lymphocytes. CLL and SLL are essentially different manifestations of the same disease and are managed in much the same way. In CLL, a significant number of the abnormal lymphocytes are found circulating in blood in addition to in bone marrow and lymphoid tissue, while in SLL, the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues few abnormal lymphocytes circulating in blood.
- 4.2 According to the Australian Institute of Health and Welfare, 1,707 Australian were diagnosed with CLL in 2015, which was expected to increase to 2,261 in 2021. The five-year relative survival rate in Australia between 2012–2016 was 83.3%.
- 4.3 The resubmission requested PBS-listing for ACA 100 mg tablets, as monotherapy or in combination with OBIN for previously untreated CLL/SLL patients.
- 4.4 Acalabrutinib is a next-generation imigazopyrazine analogue that is a highly potent and selective inhibitor that irreversibly blocks Bruton's tyrosine kinase enzyme (BTK). Its anatomical therapeutic chemical (ATC) classification is L01XE51.

5 Comparator

- 5.1 The resubmission nominated the treatment combination of venetoclax (BCL2 inhibitor) plus obinutuzumab (CD20 monoclonal antibody) as the main comparator.
- 5.2 The PBAC previously considered VTX+OBIN as an appropriate main comparator for ACA+/-OBIN (paragraph 7.6, ACA, PSD, December 2022 PBAC intracycle meeting).
- 5.3 The resubmission nominated zanubrutinib (ZANU) as a near market comparator. This drug is also an inhibitor of BTK indicated for CLL/SLL as monotherapy. This nomination was considered appropriate as the PBAC recommended the listing of ZANU for patients with treatment naïve CLL/SLL at its March 2023 meeting.

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 Rare Cancers Australia via the Consumer Comments facility on the PBS website. The comments described how the availability of an oral treatment could give back more time to patients, and lead to improved quality of life.

Clinical trials

6.3 The resubmission was based on the same two pivotal head-to-head phase 3, randomised, open-label, multicentre trials as the previous submissions; the ELEVATE-TN trial directly comparing ACA+/-OBIN with obinutuzumab plus chlorambucil (OBIN+CHL) and the CLL-14 trial that directly compared VTX+OBIN with OBIN+CHL.

6.4 For the near-market comparator, ZANU, the resubmission was based on the SEQUOIA trial, a phase 3, open-label, multicentre, randomised clinical trial comparing ZANU with bendamustine plus rituximab (BEND+RIT) in untreated CLL.

6.5 The ELEVATE-TN and CLL-14 clinical study reports and associated publications are listed in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
ELEVATE-TN NCT02475681	A randomized, multicentre, open-label, 3 arm phase 3 study of obinutuzumab in combination with chlorambucil, ACP-196 in combination with obinutuzumab, and ACP-196 monotherapy in subjects with previously untreated chronic lymphocytic leukaemia.	Interim clinical Study Report, 16 August 2019.
	A randomized, multicentre, open-label, 3 arm phase 3 study of obinutuzumab in combination with chlorambucil, acp-196 in combination with obinutuzumab, and acp-196 monotherapy in subjects with previously untreated chronic lymphocytic leukaemia	Interim Clinical Study Report, 07 September 2022.
	Xu W. ELEVATE-TN high level results (11 September 2020 data cut).	PowerPoint slides, Attachment 2D of the resubmission, 7 January 2021.
	Acerta Pharma BV. Elevate CLL TN: Study of Obinutuzumab + Chlorambucil, Acalabrutinib (ACP-196) + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL	2015; ClinicalTrials.gov/show/NCT02475681
	Gaitonde, P., B. Liljas, B. Shaw, and P. Miranda. Adjusting Survival Data for Treatment Crossover in the Elevate-Tn Trial by Using a Historical Cohort of Patients Treated with Chemoimmunotherapy in Front-Line Chronic Lymphocytic Leukemia.	Hemasphere 2022;6
	Martens U, Sharman J, Banerji V, Fogliatto LM, Herishanu Y, Munir T, et al. Elevate tn phase 3 study of acalabrutinib plus obinutuzumab or acalabrutinib monotherapy vs chlorambucil plus obinutuzumab (CLBO) in subjects with previously untreated chronic lymphocytic leukemia (CLL).	Oncology research and treatment 2020; 43(127).

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Trial ID	Protocol title/ Publication title	Publication citation
	Munir T, Sharman J, Banerji V, Fogliatto LM, Herishanu Y, Walewska R, et al. ELEVATE-TN: a phase 3, multicentre, open-label study of acalabrutinib (Ab) combined with obinutuzumab (O) or Ab alone versus O plus chlorambucil (Clb) in patients (pts) with treatment-naive chronic lymphocytic leukaemia (TN-CLL).	British Journal of Haematology 2020; 189:26-8.
	Sharman JP, Egyed M, Jurczak W, Skarbnik A, Kamdar M, Munir T, et al. Acabrutinib +/- Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 5-Year Follow-Up of ELEVATE-TN.	Hematologic malignancies—lymphoma and chronic lymphocytic leukemia 2022; Poster session 7539
	Sharman J, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acabrutinib +/- obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: elevate-TN 4-year follow-up	Hemasphere 2021; 5 (SUPPL 2): 28-9
	Sharman JP, Banerji V, Fogliatto LM, Herishanu Y, Munir T, Walewska R, et al. ELEVATE TN: phase 3 Study of Acabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL).	Blood 2019; 134 (31).
	Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. CLL-139: acalabrutinib +/- Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: ELEVATE-TN 4-Year Follow-up.	Clinical lymphoma, myeloma & leukemia 2021; 21: S318-S9.
	Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial.	Lancet 2020; 395(10232):1278-91
	Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Kamdar MK, et al. Acabrutinib +/- obinutuzumab versus obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: elevate-TN four-year follow-up.	Journal of Clinical Oncology 2021; 39 (15 SUPPL).
	Walker P, Sharman JP, Jurczak W, Munir T, Banerji V, Coutre S, et al. CN4 Patient-Reported Outcomes from the Phase 3, Randomized Study of Acabrutinib with or without Obinutuzumab Versus Chlorambucil PLUS Obinutuzumab for Treatment-Naive Chronic Lymphocytic Leukemia (ELEVATE-TN).	Value in health 2021; 24 (S3-S4.)
CLL-14	Al-Sawaf O, Zhang C, Robrecht S, Kotak A et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study.	Hemasphere 2022; 6:S3.
	Al-Sawaf, O., C. Zhang, S. Robrecht, A. Kotak, N. Chang, A. Fink, E. Tausch, et al. Cll-246 Venetoclax-Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia: 5-Year Results of the Randomized Cll14 Study.	Clinical lymphoma, myeloma & leukemia 2022; 22 (S274-S275)
	Al-Sawaf, O., C. Zhang, T. Lu, M. Liao, A. Panchal, S. Robrecht, T. Ching, et al. Utilizing Serial Minimal Residual Disease (Mrd) Assessments: Long-Term Outcomes and Insights from Modeling Mrd Growth by Next generation Sequencing (Ngs) within the Randomized Cll14 Study Evaluating Fixed duration Therapy with Venetoclax and Obinutuzumab.	Leukemia & Lymphoma 2021; 62 (SUPPL 1): S19-p.
	Al-Sawaf O, Gentile B, Devine J, Zhang C et al. Health-related quality of life with fixed-duration venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: Results from the randomized, phase 3 CLL14 trial.	American Journal of Hematology 2021; 96(9):1112-9.

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Trial ID	Protocol title/ Publication title	Publication citation
	Al-Sawaf O, Zhang C, Lu T, Liao MZ, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study.	Journal of Clinical Oncology 2021; 39(36):4049-60.
	Al-Sawaf O, Zhang C, Robrecht S, Tandon M et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomized CLL14 study.	Hematological Oncology 2021; 39 (SUPPL 2): 201-3.
	Al-Sawaf O, Zhang C, Tandon M, Sinha A et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial.	Lancet Oncology. 2020; 21(9):1188-1200.
	Al-Sawaf OM, Zhang C, Robrecht S, Wilson C, Tandon M, Ching T, et al. Clonal dynamics after venetoclax-obinutuzumab therapy: novel insights from the randomized, phase 3 CLL14 trial.	Blood 2020;136 (SUPPL 1): 22-3.
	Al-Sawaf O, Zhang C, Tandon M, Robrecht S, Sinha A, Fink AM, et al. Characteristics and outcome of patients with chronic lymphocytic leukaemia and partial response to venetoclax-obinutuzumab.	Hemasphere 2020; 4(306).
	Al-Sawaf O, Zhang C, Tandon M, Sinha A, Fink A, Robrecht S, et al. Fixed-duration venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: follow-up of efficacy and safety results from the multicenter, open-label, randomized phase 3 CLL14 trial.	Hemasphere 2020; 4:30-1.
	Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, et al. Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD-) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities.	Journal of Clinical Oncology 2019; 37.
	Fischer K, Al-Sawaf O, Fink AM, Dixon M, Bahlo J, Warburton S, et al. Safety and efficacy of venetoclax and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia (CLL) and coexisting medical conditions: final results of the run-in phase of the randomized CLL14 trial (BO25323).	Blood 2016;128(22).
	Fischer K, Al-Sawaf O, Fink AM, Dixon M, Robrecht S, Bahlo J, et al. Continuing remissions after venetoclax and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia (CLL) and coexisting medical conditions.	Hemasphere 2018; 2(127).
	Fischer K, Fink AM, Bishop H, Dixon M, Bahlo J, Choi MY, et al. Results of the safety run-in phase of CLL14 (BO25323): A prospective, open-label, multicenter randomized phase iii trial to compare the efficacy and safety of obinutuzumab and venetoclax (GDC-0199/ABT-199) with obinutuzumab and chlorambucil in patients with previously untreated cl and coexisting medical conditions.	Blood 2016; (23):496.
	Fischer K, Porro Lura M, Al-Sawaf O, Bahlo J, Fink A, Tandon M, et al. Fixed-duration venetoclax plus obinutuzumab improves pfs and minimal residual disease negativity in patients with previously untreated CLL and comorbidities.	Hematological oncology 2019; 37:82-4.
	Fischer K, Ritgen M, Al-Sawaf O, Robrecht S, Tandon M, Fink AM, et al. Quantitative analysis of minimal residual disease (MRD) shows high rates of undetectable MRD after fixed-duration chemotherapy-free treatment and serves as surrogate marker for progression-free survival: a prospective analysis of the randomized CLL14 trial.	Blood 2019;134.
	Fischer K, Al-Sawaf O, Bahlo J, Fink AM et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions.	New England Journal of Medicine 2019; 380(23):2225-36.

Trial ID	Protocol title/ Publication title	Publication citation
	Tausch E, Schneider C, Robrecht S, Zhang C et al. Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax.	Blood 2020; 135(26):2402-12.
SEQUOIA	BeiGene. A Study Comparing Zanubrutinib with Bendamustine Plus Rituximab in Participants With Previously Untreated CLL or SLL	2017
	Ghia, P.; Barnes, G.; Yang, K.; Tam, C.; Hillmen, P., et al. M. Patient-reported outcomes from a phase 3 randomized study of zanubrutinib versus bendamustine plus rituximab (br) in patients with treatment-naive (tn) cll/sll	Hemasphere 2022; 6:174-1075
	Kahl, B. S.; Giannopoulos, K.; Jurczak, W.; Scaronimkovic, M.; Shadman, M.; et al. CLL-137 SEQUOIA: results of a Phase 3 Randomized Study of Zanubrutinib Versus Bendamustine + Rituximab (BR) in Patients With Treatment-Naive (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/ SLL)	Clinical lymphoma, myeloma & leukemia 2022; 22 (2): S269-S270
	Munir, T.; Giannopoulos, K.; Jurczak, W.; Simkovic, M.; Shadman, M et al. SEQUOIA: results of a Phase 3 Randomised Study of Zanubrutinib versus Bendamustine + Rituximab in Patients with Treatment-Naive Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma	British Journal of Haematology 2022; 197 (SUPPL1): 95-96
	Tam, C. S.; Giannopoulos, K.; Jurczak, W.; Simkovic, M.; Shadman, M. et al. SEQUOIA: results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab (BR) in Patients with Treatment-Naive (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)	Blood 2021; 138 (396): 2021-2022
	Tam, C. S.; Robak, T.; Ghia, P.; Kahl, B. S.; Walker, P., et al. Efficacy and safety of zanubrutinib in patients with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): initial results from arm C of the sequoia (BGB-3111-304) trial	Blood 2019; 134 (SUPPL1)
	Tam, C. S.; Brown, J. R.; Kahl, B. S.; Ghia, P.; Giannopoulos, K. et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial	Lancet Oncology 2022; 23 (8): 1031-1043

Source: Table 2.5, p.76-79 and Attachment 2X_ZANU Search Outcomes of the resubmission

6.6 The key features of ELEVATE-TN, CLL-14 and SEQUOIA trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
ACA+/-OBIN versus OBIN+CHL					
ELEVATE-TN	535	R, MC, OL 58.2 months FU	Unclear*	Previously untreated CLL/SLL	INV-PFS, IRC-PFS, OS, AEs
VTX+OBIN versus OBIN+CHL					
CLL-14	432	R, MC, OL 52.4 months FU	Unclear*	Previously untreated CLL/SLL	INV-PFS, IRC-PFS, OS, AEs
ZANU versus BEND+RIT					
SEQUOIA	590	R, MC, OL 26.2 months FU	Unclear	Previously untreated CLL/SLL	INV-PFS, IRC-PFS, OS, AEs

Source: Table 2.24, pp.110-111, Table A1.1 p.1 of the resubmission and Table 4, p.14 of the commentary for the PBAC December 2022 intracycle meeting

ACA = acalabrutinib, AE = adverse events, BEND = bendamustine, CHL = chlorambucil, FU = follow-up, INV = investigator, IRC = Independent Review Committee, MC = multicentre, OBIN = obinutuzumab, OL = open label, OS = overall survival, PFS = progression-free survival, R = randomised, RIT = rituximab, VTX = venetoclax, ZANU = zanubrutinib

*PBAC December 2022 meeting (paragraph 6.10, ACA, PSD, December 2022 PBAC intracycle meeting)

Comparative effectiveness: ACA+/-OBIN versus VTX+OBIN

- 6.7 As no head-to-head trials were available comparing ACA+/-OBIN versus VTX+OBIN, the resubmission presented an updated anchored MAIC for PFS and OS comparing ACA+/-OBIN (ELEVATE-TN trial, 58.2-month median follow-up) to VTX+OBIN (CLL-14 trial, 52.4-months median follow-up).
- 6.8 The MAIC was anchored on chlorambucil plus obinutuzumab (CHL+OBIN) as the common comparator in both trials. The ELEVATE-TN trial compared ACA monotherapy, ACA+OBIN and CHL+OBIN, while the CLL-14 trial compared VTX+OBIN and CHL+OBIN.
- 6.9 The individual trial results for the ELEVATE-TN and the CLL-14 trials were presented in the previous resubmission.
- 6.10 The previous resubmission presented a MAIC for ACA+OBIN versus VTX+OBIN for effectiveness and safety, based on shorter median follow-up (46.9 months and 39.6 months respectively). At its December 2022 intracycle meeting (paragraph 6.39, ACA, PSD, December 2022 PBAC meeting), the PBAC noted that:
- To conserve the effective sample size (ESS), the MAIC matched fewer variables compared with the original MAIC.
 - Age, sex, 17p deletion status, complex karyotype status and CIRS score were not matched, and the resubmission did not adequately justify the decision to exclude from matching relevant variables.
 - The MAICs presented in July 2020 effectively excluded 96 patients in the ACA+OBIN arm and 83 in ACA. In the December 2022 resubmission the updated MAICs excluded 7 and 3 patients in each arm. The resubmission did not adequately address the reasons for this difference.
 - The ESC considered that the MAIC should adjust for all effect modifiers and prognostic variables to predict outcomes reliably.
 - The ESC considered that the failure to match important prognostic variables suggested that the results of the MAICs were unlikely to be reliable.
- 6.11 For the current updated MAIC, the resubmission stated:
- The baseline characteristics before and after matching between ACA+/-OBIN and VTX+OBIN were not available.
 - Treatment effect modifiers were chosen by fitting a Cox model with interactions for each potential effect modifier and treatment.
 - Backwards stepwise selection was used with a p-value threshold of 0.2 to remove variables without a statistically significant treatment interaction.
 - Significant effect modifiers identified for ACA+/-OBIN remained in the analysis.

- 6.12 Given that the resubmission did not present patient characteristics before and after matching, it was not possible to analyse the adequateness of this matching and whether the effect modifiers selected for inclusion in the MAIC were appropriate.
- 6.13 The resubmission did not address the request made by the PBAC that the MAIC should adjust for all effect modifiers and prognostic variables to reliably predict outcomes. The Pre-Sub-Committee Response (PSCR) stated only significant treatment effect modifiers identified for ACA+/-OBIN remained in the updated MAIC analyses to maintain a robust sample size and considered the variables that did not meet the p-value threshold of 0.2 (age ≥ 65 years, sex, Del 17p, complex karyotype and CIRS>6) were not likely to be treatment effect modifiers. The PSCR considered that matching for these additional variables would not be expected to significantly change the conclusion of the MAIC.
- 6.14 The treatment effect modifier variables identified using the Cox model, which remained in the analysis and that were included in the MAIC, are presented in Table 5.

Table 5: Treatment effect modifiers - Cox model

Treatment	Endpoint	Significant effect modifiers
ACA+OBIN	OS	B2 ≤ 3.5 mg/L, IPI risk ≥ high, Rai stage 3 or 4, TP53 deleted or mutated
ACA+OBIN	PFS	Age, B2 ≤ 3.5 mg/L, creatinine clearance < 70 mL/min, IGHV unmutated, Rai stage 3 or 4
ACA+OBIN	TTNT	Age, creatinine clearance < 70 mL/min, deletion in 11q, IGHV unmutated, Rai stage 3 or 4
ACA mono	OS	Rai stage 3 or 4, TP53 deleted or mutated
ACA mono	PFS	Age, deletion in 11q, IGHV unmutated, Rai stage 3 or 4, TP53 deleted or mutated
ACA mono	TTNT	Age, creatinine clearance < 70 mL/min, IGHV unmutated, IPI-GEHI, Rai stage 3 or 4

Source: Table 2.86, p.191 of the resubmission

ACA = acalabrutinib, B2 = serum B2, IPI risk = International Prognostic Index for Diffuse Large B-cell Lymphoma, TP53 = tumour protein P53, IGHV = immunoglobulin heavy chain variable region genes, 11q= long arm (q) of chromosome 11, OBIN = obinutuzumab, OS = overall survival, PFS = progression free survival, TTNT = time to the next treatment

- 6.15 The resubmission presented effective sample sizes (ESS) after excluding variables without a statistically significant treatment interaction based on the Cox model. These ESS are shown in Table 6.

Table 6: Effective sample sizes (ESS) in MAIC update of ACA+/-OBIN (58.2-month median follow-up) vs VTX+OBIN (52.4-month median follow-up)

Treatment	Endpoint	N		ESS	
		OBIN+CHL	ACA	OBIN+CHL	ACA
ACA+OBIN	OS	177	179	126.8	123.8
ACA+OBIN	PFS	177	179	144.5	143.2
ACA mono	OS	177	179	167.5	168.6
ACA mono	PFS	177	179	175.0	177.9

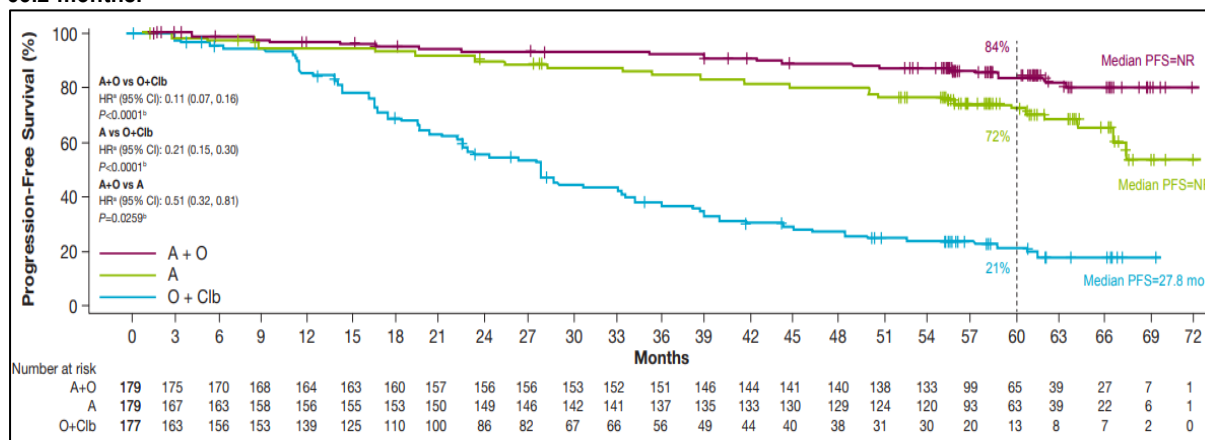
Source: Table 2.87, p.191 of the resubmission

ACA = acalabrutinib, CHL = chlorambucil, MAIC = matching adjusted indirect comparison, OBIN = obinutuzumab, OS = overall survival, PFS = progression free survival, mono = monotherapy

Indirect Comparison of Effectiveness

- 6.16 The PFS results from the ELEVATE-TN trial (58.2 month follow-up) and the CLL-14 trial (52.4 month follow-up) are presented in Figure 1 and Figure 2. These data were included in the previous resubmission.

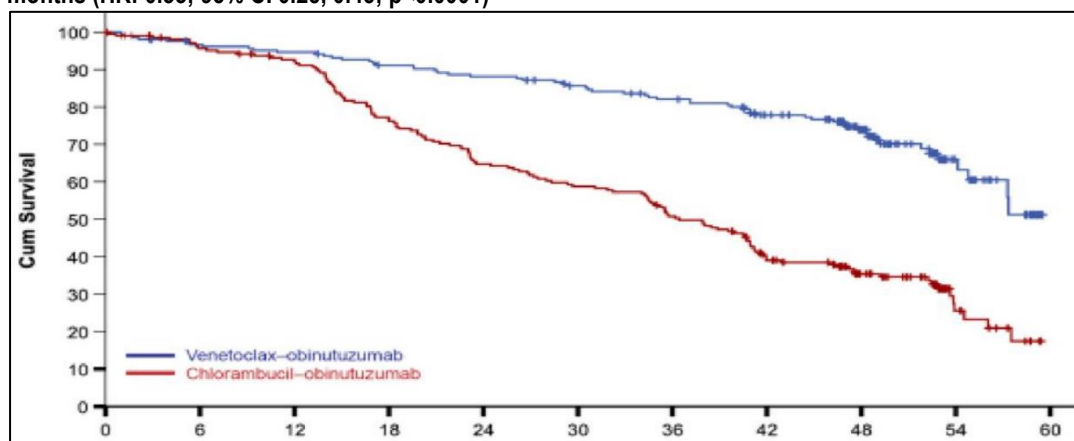
Figure 1 Kaplan-Meier Plot for investigator-assessed PFS (ITT Population) in ELEVATE-TN at median follow-up of 58.2-months.



Source: Figure 2.4, p.117 of the resubmission

A= acalabrutinib, O= obinutuzumab NR= not reported, Clb= chlorambucil, PFS= progression-free survival

Figure 2 Kaplan-Meier Plot for investigator-assessed PFS (ITT Population) in CLL-14 at median follow-up of 52.4-months (HR: 0.33; 95% CI 0.25, 0.45; p<0.0001)



Source: Figure 2.5, p.120 of the resubmission

A= acalabrutinib, O= obinutuzumab NR= not reported, Clb= chlorambucil, PFS= progression-free survival

6.17 The comparative effectiveness for PFS and OS, based on the updated MAIC is presented in Table 7.

Table 7: Results of the updated MAIC of ACA+/-OBIN (58.2-month median follow-up) vs VTX+OBIN (52.4-month median follow-up)

Effectiveness outcomes	ACA vs VTX+OBIN	ACA+OBIN vs VTX+OBIN
Progression free survival (PFS): HR (95% CI)		
Unweighted	0.65 (95% CI: 0.41, 1.01)	0.34 (95% CI: 0.20, 0.56)
Weighted	0.65 (95% CI: 0.41, 1.03)	0.29 (95% CI: 0.17, 0.52)
Overall survival (OS): HR (95% CI)		
Unweighted	1.19 (95% CI: 0.60, 2.37)	0.69 (95% CI: 0.32, 1.45)
Weighted	1.13 (95% CI: 0.56, 2.24)	0.68 (95% CI: 0.31, 1.50)

Source: Table 2.90, p.195 and Table 2.93, p.198 of the resubmission

ACA = acalabrutinib, CI = confidence interval, HR = hazard ratio, MAIC = matching adjusted indirect comparison, OBIN = obinutuzumab, VTX = venetoclax

Bold = statistically significant

- 6.18 Based on the MAIC patients treated with ACA+OBIN had a statistically significant 71% reduction in the risk of progression or death (PFS) compared to VTX+OBIN (HR: 0.29 [95% CI: 0.17, 0.52] for the weighted analysis and HR: 0.34 [95% CI: 0.17, 0.52] for the unweighted analysis). Patients treated with ACA monotherapy had a 35% reduction in the risk of progression or death (PFS) compared to VTX+OBIN; however, this was not statistically significant based on both the weighted (HR= 0.65 [95% CI: 0.41, 1.03]) and unweighted (HR= 0.65 [95% CI: 0.41, 1.01]) comparisons.
- 6.19 In terms of OS, comparing ACA monotherapy to VTX+OBIN, the results favoured VTX+OBIN, for both the weighted (HR= 1.13 [95% CI: 0.56, 2.24]) and unweighted (HR= 1.19 [95% CI: 0.56, 2.24]) comparisons, but the differences were not statistically significant. Comparing ACA+OBIN to VTX+OBIN, the OS results favoured ACA+OBIN, however these differences were also not statistically significant, for both the weighted (HR= 0.68 [95% CI: 0.31, 1.50]) and unweighted (HR= 0.69 [95% CI: 0.32, 1.45]) comparisons. The ESC noted the wide confidence intervals for the OS hazard ratios reflect the indolent nature of CLL and hence the small number of death events.
- 6.20 Based on these results, the resubmission stated that the updated MAIC based on ACA at 58.2-month of follow-up compared to VTX+OBIN at 52.4-month of follow-up demonstrated that ACA+/-OBIN is non-inferior in terms of efficacy, compared to VTX+OBIN. These results should be considered with caution because baseline characteristics before and after matching were not provided and the MAIC did not match for all treatment effect modifiers as the PBAC requested.

Comparative harms: ACA+/-OBIN versus VTX+OBIN

- 6.21 The safety data for ACA+/-OBIN versus OBIN+CHL in ELEVATE-TN for median follow-up of 28.3, 46.9 and 58.2-months was presented in the submission considered at the December 2022 PBAC meeting. The adverse event (AE) profile of VTX+OBIN versus OBIN+CHL from the CLL-14 trial with median follow-up of 28.1 and 39.6 months was also presented for the previous submission.
- 6.22 An updated MAIC of safety outcomes based on a 58.2-month median follow-up was not presented however, the resubmission stated that the safety results at 58.2 and

39.6-months follow-up in ELEVATE-TN and CLL-14 were consistent with previous analyses.

- 6.23 No detailed safety analyses have been reported after the 39.6 months of follow-up for CLL-14, which limited performing an updated MAIC for safety outcomes based on a longer follow-up. Therefore, safety results should be considered with caution.
- 6.24 Data from events of clinical interest, grade 3 or higher treatment-emergent adverse events, and treatment-related adverse events were not available from the CLL-14 trial at any follow-up. Data on the most common AEs, treatment-related AEs, deaths, and AEs that led to discontinuation were only available for 39.6 months of follow-up, but not for the longer periods of 52.4 months or 65.4 months.

Safety results: from the whole trial population

6.25 A summary of key AEs comparing CLL-14 and ELEVATE-TN is presented in Table 8.

Table 8: Summary of key adverse events comparing the CLL-14 and ELEVATE-TN trials

AEs	ELEVATE-TN			CLL-14			
	ACA (N=179)	ACA+OBIN (N=178)	OBIN+CHL (N=169)	VTX+OBIN (N=212)	OBIN+CHL (N=214)	VTX+OBIN (N=212)	OBIN+CHL (N=214)
Median follow-up, months	58.2			39.6		52.4	
Any AE, n (%)	173 (96.6)	176 (98.9)	167 (98.8)	201 (94.8)	213 (99.5)	NR	NR
≥1 Grade ≥3 TEAE, n (%)	113 (63.1)	143 (80.3)	121 (71.6)	150 (70.8)	155 (72.4)	NR	NR
SAEs, n (%)	77 (43.0)	95 (53.4)	37 (21.9)	115 (54.2)	95 (44.4)	NR	NR
AE leading to death, n (%)	18 (10.1)	11 (6.2)	12 (7.1)	19 (8.8)	11 (5.1)	23 (10.6)	14 (6.5)

Source: Table ES9, p. xxv of the resubmission executive summary

ACA = acalabrutinib, AE = adverse event, CHL = chlorambucil, NR = not reported, OBIN = obinutuzumab, SAE = serious adverse event, TEAE = treatment-emergent adverse event, VTX = venetoclax

- 6.26 Overall, individual safety results from the ELEVATE-TN trial at 58.2 months of follow-up and the CLL-14 trial at 39.6 and 52.4 months of follow-up did not support a claim of superiority for ACA+/-OBIN compared with VTX+OBIN.
- 6.27 The trial results showed that patients treated with ACA at 58.2 months median follow-up had a lower proportion of Grade ≥3 TEAEs than VTX+OBIN at 39.6 months median follow-up (63.1% vs 70.8%), while patients treated with ACA+OBIN had a higher proportion (80.3% vs 70.8%). For the longer VTX+OBIN follow-up of 52.4 months, patients treated with ACA had a similar proportion of AEs leading to death to VTX+OBIN (10.1% vs 10.6%), while ACA+OBIN had a lower proportion (6.2% vs 10.6%).
- 6.28 A summary of adverse events in the ELEVATE-TN and CLL-14 trials are presented in Table 9 and Table 10 respectively.

Table 9: Summary of key adverse events in the ELEVATE-TN trial for 58.2-months of follow-up

ELEVATE-TN	ACA (N=179)		ACA+OBIN (N=178)		OBIN+CHL (N=169)	
Most common AEs (≥25% of patients), n (%)						
AEs Grades	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 AE	173 (96.6)	113 (63.1)	176 (98.9)	143 (80.3)	167 (98.8)	121 (71.6)
Diarrhoea	76 (42.5)	1 (0.6)	77 (43.3)	10 (5.6)	36 (21.3)	3 (1.8)
Headache	70 (39.1)	2 (1.1)	72 (40.4)	2 (1.1)	20 (11.8)	0
Neutropenia	22 (12.3)	20 (11.2)	60 (33.7)	55 (30.9)	77 (45.6)	71 (42.0)
Upper respiratory tract infection	47 (26.3)	0	45 (25.3)	4 (2.2)	16 (9.5)	1 (0.6)
Nausea	44 (24.6)	0	44 (24.7)	0	53 (31.4)	0
Infusion-related reaction	1 (0.6)	0	26 (14.6)	5 (2.8)	69 (40.8)	10 (5.9)
Fatigue	43 (24.0)	2 (1.1)	52 (29.2)	4 (2.2)	30 (17.8)	2 (1.2)
Contusion	31 (17.3)	0	47 (26.4)	0	7 (4.1)	0
Arthralgia	47 (26.3)	2 (1.1)	60 (33.7)	4 (2.2)	10 (5.9)	2 (1.2)
Events of clinical interest, n (%)						
AEs Grades	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	39 (21.8)	18 (10.1)	43 (24.2)	17 (9.6)	13 (7.7)	3 (1.8)
Atrial fibrillation	13 (7.3)	2 (1.1)	11 (6.2)	2 (1.1)	1 (0.6)	0
Hypertension	16 (8.9)	7 (3.9)	17 (9.6)	8 (4.5)	6 (3.6)	5 (3.0)
Bleeding	78 (43.6)	6 (3.4)	88 (49.4)	8 (4.5)	20 (11.8)	0
Major bleeding	8 (4.5)	6 (3.4)	12 (6.7)	8 (4.5)	2 (1.2)	0
Infections	135 (75.4)	35 (19.6)	140 (78.7)	50 (28.1)	75 (44.4)	14 (8.3)
Second primary malignancies*	17 (9.6)	12 (6.7)	17 (9.6)	12 (6.7)	3 (1.8)	2 (1.2)
Serious adverse events, n (%)						
AEs Grades	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Subjects with ≥1 SAE	77 (43.0)	72 (40.2)	95 (53.4)	83 (46.6)	37 (21.9)	33 (19.5)
Pneumonia	11 (6.1)	10 (5.6)	12 (6.7)	8 (4.5)	3 (1.8)	3 (1.8)
COVID-19	4 (2.2)	2 (1.1)	7 (3.9)	7 (3.9)	0	0
Infusion-related reaction	0	0	4 (2.2)	3 (1.7)	2 (1.2)	2 (1.2)
Anaemia	5 (2.8)	5 (2.8)	3 (1.7)	3 (1.7)	0	0
Febrile neutropenia	2 (1.1)	2 (1.1)	3 (1.7)	3 (1.7)	7 (4.1)	7 (4.1)
Dyspnoea	4 (2.2)	4 (2.2)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Respiratory tract infection	4 (2.2)	4 (2.2)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Tumour lysis syndrome	0	0	1 (0.6)	1 (0.6)	8 (4.7)	8 (4.7)

Source: Table 2.53, p.153, Table 2.58, p.157, Table 2.61, p.159, Table 2.66, pp.164-165, Table 2.568 p.167, Table 2.71, p.170, Table 2.74, p.174, Table 2.79, p.177 of the resubmission.

ACA = acalabrutinib, AEs = adverse events, CHL = chlorambucil, OBIN = obinutuzumab, SAE = serious adverse event, VTX = venetoclax

*Excluding nonmelanoma skin cancer (NMSC)

Table 10: Summary of key adverse events in the CLL-14 trial for 39.6-months of follow-up

CLL-14	VTX+OBIN (N=212)		OBIN+CHL (N=214)	
Most common AEs (≥25% of patients), n (%)				
AEs Grades	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event	201 (94.8)	150 (70.8)	213 (99.5)	155 (72.4)
Neutropenia	122 (57.5)	112 (52.8)	121 (56.5)	102 (47.7)
Infusion-related reaction	96 (45.3)	22 (10.4)	117 (54.7)	22 (10.3)
Diarrhoea	58 (27.4)	8 (3.7)	34 (15.9)	1 (0.5)
Serious adverse events, n (%)				
AEs Grades	Any Grade		Any Grade	
Subjects with ≥1 SAE	115 (54.2)		95 (44.4)	
VTX related SAE	30 (14.2)		NR	
Infections	10 (4.7)		12 (5.6)	
OBIN related SAE	39 (18.4)		50 (23.4)	
Infusion-related reaction	10 (4.7)		12 (5.6)	
Febrile neutropenia	9 (4.2)		NR	
Infections	NR		12 (5.6)	

Source: Table 2.55, pp. 154-155, Table 2.64, p. 161, Table 2.77, p. 175 of the resubmission

ACA = acalabrutinib, AEs = adverse events, CHL = chlorambucil, NR = not reported, OBIN = obinutuzumab, SAE = serious adverse events, VTX = venetoclax

Safety results: indirect comparison

6.29 The MAIC safety outcomes for ACA (46.9-month median follow-up) vs VTX+OBIN (39.6-month median follow-up) are presented in Table 11 and Table 12.

Table 11: Safety outcomes MAIC update for ACA (46.9-month median follow-up) vs VTX+OBIN (39.6-month median follow-up)

Grade ≥3 adverse event	Before matching		After matching		Risk difference (95% CI), p-value
	ACA N=176 ^a	VTX+OBIN N=216	ACA N=96	VTX+OBIN N=216	
Anaemia	NR	NR	8.7%	8%	-0.7 (-6.3, 7.6), p=0.841
Diarrhoea	NR	NR	1.0%	3.8%	-2.8 (-6.0, 0.5), p=0.1
Febrile neutropenia	NR	NR	0.3%	5.2%	-4.9 (-8.0, -1.9), p=0.002*
Infusion-related reaction	NR	NR	0%	9%	-9.0 (-12.9, -5.1), p<0.001*
Leukopenia	NR	NR	0%	2.4%	-2.4 (-4.5, -0.3), p=0.029
Neutropenia	NR	NR	9%	52.8%	-43.8 (-52.0, -35.5), p<0.001*
NMSC	NR	NR	0.4%	8%	-7.6 (-11.3, -3.9), p<0.001*
Pneumonia	NR	NR	4.3%	5.7%	-1.4 (-6.1, 3.4), p=0.56
SPM (excluding NMSC)	NR	NR	3%	9%	-6.0 (-11.1, -1.0), p=0.021*
Thrombocytopenia	NR	NR	2.2%	13.7%	-11.5 (-16.6, -6.4), p<0.001*
Tumour lysis syndrome	NR	NR	0%	1.4%	-1.4 (-3.0, 0.2), p=0.08

Source: Table 2.97, p. 196 of the resubmission

ACA = acalabrutinib, CI = confidence interval, ESS = effective sample size, MAIC = matching adjusted indirect comparison, NMSC = non melanoma skin cancer, NR = not reported, OBIN = obinutuzumab, SPM = secondary primary malignancy, VTX = venetoclax.

* denotes p-value <0.05: In bold

^a Pre-match N does not necessarily match N of ELEVATE-TN due to incomplete baseline data recording for some patients in outcomes.

Table 12: Safety outcomes MAIC update for ACA+OBIN (46.9-month median follow-up) vs VTX+OBIN (39.6-month median follow-up)

Grade ≥3 adverse event	Before matching		After matching		Risk difference (95% CI), p-value
	ACA+OBIN N N=172 ^a	VTX+OBIN N N=216	ACA+OBIN N=104	VTX+OBIN N=216	
Anaemia	NR	NR	6.0%	8.0%	-2.0 (-7.4, 3.3), p=0.459
Diarrhoea	NR	NR	3.5%	3.8%	-0.3 (-4.1, 3.5), p=0.875
Febrile neutropenia	NR	NR	3.3%	5.2%	-1.9 (-6.4, 2.5), p=0.409
Infusion-related reaction	NR	NR	1.4%	9.0%	-7.6 (-11.8, -3.4), p<0.001*
Leukopenia	NR	NR	0.2%	2.4%	-2.2 (-4.3, -0.1), p=0.046*
Neutropenia	NR	NR	29.1%	52.8%	-23.7 (-34.5, -12.8), p<0.001*
NMSC	NR	NR	1.3%	8.0%	-6.7 (-10.7, -2.7), p=0.001*
Pneumonia	NR	NR	7.3%	5.7%	1.6 (-4.7, 8.0), p=0.617
SPM (excluding NMSC)	NR	NR	5.3%	9.0%	-3.7 (-10.0, 2.6), p=0.248
Thrombocytopenia	NR	NR	9.6%	13.7%	-4.1 (-11.2, 3.1), p=0.268
Tumour lysis syndrome	NR	NR	1.4%	1.4%	0 (-2.4, 2.4), p=1

Source: Table 2.98, p. 197 of the resubmission.

ACA = acalabrutinib, CI = confidence interval, ESS = effective sample size, MAIC = matching adjusted indirect comparison, NMSC = non melanoma skin cancer, NR = not reported, OBIN = obinutuzumab, SPM = secondary primary malignancy, VTX = venetoclax.

* denotes p-value <0.05: In bold

^a Pre-match N does not necessarily match N of ELEVATE-TN due to incomplete baseline data recording for some patients in outcomes.

- 6.30 Based on the MAIC, ACA monotherapy compared to VTX+OBIN was associated with statistically significantly fewer events of Grade 3-4 febrile neutropenia (0.3% vs 5.2%, p=0.002), infusion-related reactions (0% vs 9%, p<0.001), neutropenia (9% vs 52.8%, p<0.001), non-melanoma skin cancer (0.4% vs 8%, p<0.001), secondary primary malignancy (3% vs 9%, p<0.021), and thrombocytopenia (2.2% vs 13.7%, p<0.001).
- 6.31 ACA+OBIN compared to VTX+OBIN was associated with statistically significantly fewer events of Grade 3-4 infusion-related reactions (1.4% vs 9.0%, p<0.001), leukopenia (0.2% vs 2.4%, p=0.046), neutropenia (29.1% vs 52.8%, p<0.001) and non-melanoma skin cancer (2.3% vs 8.0%, p=0.001) compared to VTX+OBIN.
- 6.32 The PBAC at its December 2022 meeting considered that these results should be interpreted with caution due to inadequate justification for the application of the MAIC methodology to specific AEs, the limited matching of prognostic variables and differences in follow-up durations in the data-cuts used (paragraph 6.50, ACA, PSD, December 2022 PBAC meeting).

Comparative effectiveness: ACA+/-OBIN versus ZANU

- 6.33 The resubmission presented an unanchored unmatched (naïve) comparison of ACA+/-OBIN and ZANU based on the ELEVATE-TN and SEQUOIA trials. The control arms in the two trials differed, OBIN+CHL in ELEVATE-TN and BEND+RIT in SEQUOIA. The PFS and OS results from ELEVATE-TN (median follow-up of 28.0-28.5 months) and SEQUOIA for the population without 17p deletion status (median follow-up of 26.2-30.5 months) are presented in Table 13 and Table 14.

Table 13: Comparison of PFS in ELEVATE-TN and SEQUOIA without 17p deletion status

PFS	ELEVATE-TN			SEQUOIA	
	ACA	ACA+OBIN	OBIN+CHL	ZANU	BEND+RIT
N	179	177	179	241	238
Median follow-up, months	28.4	28.5	28.0	30.5	26.2
IRC PFS					
n/N (%)	26 (14.5)	14 (7.8)	93 (52.5)	36 (14.9)	71 (29.8)
Median time to event (95% CI)	NR	NR	NR	NR	NR
HR (95% CI)* p-value (log-rank test)	0.20 (0.13, 0.30) <0.0001	0.10 (0.06, 0.17) <0.0001	NA	0.42 (0.28, 0.63) <0.0001	NA
24-month PFS rate, % (95% CI)	87.3 (80.9, 91.7)	92.7 (87.4, 95.8)	46.7 (38.5, 54.6)	85.5 (80.1, 89.6)	69.5 (62.4, 75.5)
INV PFS					
n/N (%)	19 (10.6)	15 (8.4)	86 (48.6)	29 (12.0)	57 (23.9)
Median time to event (95% CI)	NR	NR	NR	NR	NR
HR (95% CI)* p-value (log-rank test)	0.16 (0.10, 0.27) <0.0001	0.12 (0.07–0.21) <0.0001	NR	0.42 (0.27, 0.66) 0.00011	NR
24-month PFS rate, % (95% CI)	90.4 (84.9, 94.0)	91.9 (86.7, 95.1)	54.7 (46.7, 62.0)	87.7 (82.1, 91.6)	76.5 (69.6, 82.1)

Source: Table 2.100, p.201 of the resubmission

ACA= acalabrutinib, BEND= bendamustine, CHL= chlorambucil, INV= investigator-assessment, IRC= independent review com, NR= not reported, OBIN= obinutuzumab, PFS= progression-free survival, RIT= rituximab, ZANU= zanubrutinib, HR = hazard ratio

Table 14: Comparison of OS in ELEVATE-TN and SEQUOIA without 17p deletion status

OS	ELEVATE-TN			SEQUOIA	
	ACA	ACA+OBIN	OBIN+CHL	ZANU	BEND+RIT
N	179	179	177	241	238
Median follow-up, months	28.4	28.5	28.0	26.2	26.2
Patients who have died, n (%)	11 (6.1)	9 (5.0)	17 (9.6)	16 (6.7)	14 (6.2)
Median OS, months (95% CI)	NtR	NtR	NtR	NtR	NtR
HR (95% CI) p-value (log-rank test)	0.60 (0.28, 1.27) 0.1556	0.47 (0.21, 1.06) 0.0577	NR	NR	NR
24-month OS rate, % (95% CI)	94.7 (90.2, 97.2)	94.9 (90.5, 97.3)	91.7 (86.3, 95.0)	94.3 (90.4, 96.7)	94.6 (90.6, 96.9)

Source: Table 2.100, p.201 of the resubmission

ACA= acalabrutinib, BEND= bendamustine, CHL= chlorambucil, NtR= not reached, NR= not reported, OBIN= obinutuzumab, RIT= rituximab, ZANU= zanubrutinib, HR = hazard ratio

Comparative harms: ACA+/-OBIN versus ZANU

6.34 The safety results from ELEVATE-TN and SEQUOIA are presented in Table 15.

Table 15: Comparison of AEs in ELEVATE-TN and SEQUOIA

AEs	ELEVATE-TN			SEQUOIA		
	ACA (SP)	ACA+OBIN (SP)	OBIN+CHL (SP)	ZANU w/o del(17p)	ZANU w del(17p)	BEND+RIT
N	179	178	169	240	111	227
Median duration of follow-up, months	28.4	28.5	28.0	26.4	30.0	25.9
Grade 3 or 4 AE, n (%)	89 (49.7)	125 (70.2)	118 (69.8)	39 (16.3)	19 (17.1)	43 (18.9)
SAEs, n (%)	57 (31.8)	69 (38.8)	37 (21.9)	88 (36.7)	45 (40.5)	113 (49.8)
TRAEs, n (%)	118 (65.9)	144 (80.9)	154 (91.1)	224 (93.3)	109 (98.2)	214 (94.3)
Discontinuation due to AEs, n (%)	17 (9.5)	30 (15.8)	34 (20.1)	20 (8.3)	6 (5.4)	31 (13.7)
AE leading to death, n (%)	6 (3.4)	4 (2.2)	10 (5.9)	11 (4.6)	3 (2.7)	11 (4.8)
Any AE, n (%)	170 (95.0)	171 (96.1)	167 (98.8)	224 (93.3)	109 (98.2)	218 (96.0)

Source: Table 2.105, p.206 of the resubmission

ACA= acalabrutinib, BEND= bendamustine, CHL= chlorambucil, OBIN= obinutuzumab, RIT= rituximab, ZANU= zanubrutinib, SAEs= serious adverse events, SP= safety population, TRAEs= treatment related adverse events, w/o= without, w=with

Benefits/harms

6.35 A benefits and harms table was not presented as the submission made a claim of non-inferiority for effectiveness.

Clinical claim

6.36 The resubmission described ACA+/-OBIN as non-inferior in terms of effectiveness compared with VTX+OBIN and superior in terms of safety compared to VTX+OBIN in patients with previously untreated CLL/SLL.

6.37 The ESC considered the effectiveness claim was likely supported but with a high degree of uncertainty due to a lack of transparency regarding the details of the MAIC, and potentially lack of appropriate adjustment of effect modifiers in the MAIC.

6.38 For the claim of superior safety, the issues regarding the MAIC methodology presented in the previous submission remained, introducing uncertainty to the results. Individual trial safety results also showed some inconsistencies that made the claim of safety superiority uncertain. Patients treated with ACA+OBIN at 58.2 months median follow-up had a higher proportion of Grade ≥3 TEAEs than VTX+OBIN at 39.6 months median follow-up, while ACA showed a lower proportion. Regarding AEs leading to death for the available longest VTX+OBIN follow-up of 52.4 months, patients treated with ACA+OBIN had a lower proportion of AEs leading to death than VTX+OBIN, while patients treated with ACA had a similar proportion. No other detailed safety analyses have been reported after the 39.6 months of follow-up data for CLL-14, which limited performing an updated MAIC for safety outcomes based on a longer follow-up. The ESC considered the resubmission's claim of superiority was not supported and a claim of non-inferior safety would be more appropriate. The pre-PBAC response stated that the sponsor pragmatically accepted a clinical claim of non-inferior safety for ACA+/-OBIN compared to VTX+OBIN in this patient population.

6.39 The PBAC considered that the claim of non-inferior comparative effectiveness of ACA +/- OBIN compared to VTX+OBIN was reasonable, with a high degree of uncertainty given the issues identified surrounding the MAIC. The PBAC considered that the claim

of non-inferior comparative effectiveness of ACA+/- OBIN compared to ZANU was likely reasonable.

- 6.40 The PBAC considered that the claim of superior comparative safety of ACA+/-OBIN compared to VTX+OBIN was not adequately supported by the data and noted that the sponsor had agreed to pragmatically accept a claim of non-inferior safety in their pre-PBAC response. The PBAC considered that the claim of non-inferior comparative safety of ACA+/- OBIN compared to ZANU was likely reasonable.

Economic analysis

- 6.41 The resubmission employed a cost-minimisation approach (CMA) of ACA+/-OBIN versus VTX+OBIN in patients with previously untreated CLL/SLL. The CMA was undertaken assuming a relative uptake ratio of 90%/10% for ACA monotherapy/ACA+OBIN. The previous resubmission presented a cost-effectiveness analysis between ACA+OBIN versus VTX+OBIN.
- 6.42 The ESC considered that the assumption of 90% ACA monotherapy use in clinical practice was not well justified. The ESC acknowledged the uncertainty in the monotherapy – combination therapy split but considered that the use of ACA monotherapy is likely to account for the majority of use given the lack of a substantial clinical benefit and increased toxicity with the addition of OBIN. The ESC suggested that a 80% - 90% ACA monotherapy/10% - 20% ACA+OBIN split would be appropriate. The pre-PBAC response stated that the sponsor has received very few requests for access to ACA+OBIN, and regular requests for access to ACA monotherapy and that they established a patient access program for ACA monotherapy in early June 2023. The pre-PBAC response further stated that the sponsor believes that while ACA+OBIN should remain a treatment option for suitable patients, combination use is expected to be small. For the purposes of deriving a weighted price for ACA+/-OBIN, the sponsor proposed a split of 85% ACA monotherapy/15% ACA+OBIN combination therapy.
- 6.43 The CMA was consistent with the claim of non-inferior efficacy and aligned with previous feedback from the PBAC in December 2022.
- 6.44 The resubmission presented the equi-effective doses as:
- ACA monotherapy: ACA 100 mg twice daily until disease progression or unacceptable toxicity is equi-effective to a combination of VTX 400 mg daily (following an initial dose up-titration over the first 5 weeks) until disease progression or unacceptable toxicity for a maximum of 12 cycles plus OBIN 1000 mg (following an initial dose up-titration over the first two doses) for a maximum of 6 cycles.
 - ACA+OBIN: ACA 100 mg twice daily until disease progression or unacceptable toxicity plus OBIN 1000 mg (following an initial dose up-titration over the first two doses) for a maximum of 6 cycles is equi-effective to a combination of VTX 400 mg daily (following an initial dose up-titration over the first 5 weeks) until disease progression or unacceptable toxicity for a maximum of 12 cycles plus OBIN

1000 mg (following an initial dose up-titration over the first two doses) for a maximum of 6 cycles.

- 6.45 Based on the economic model provided by the resubmission, the equi-effective doses were adjusted as per actual mean doses administered in the trials:
- 293,000 mg of ACA plus 7,553 mg of OBIN is equi-effective to 90,883 mg of VTX plus 7,355 mg of OBIN.
 - 284,100 mg of ACA is equi-effective to 90,883 mg of VTX plus 7,355 mg of OBIN.
- 6.46 The equi-effective doses were based on the cumulative dose patients received in the ELEVATE-TN trial, up to the 58.2-month cut-off, for ACA+/-OBIN and the CLL-14 trial for VTX+OBIN. Given that a significant proportion of participants remained on treatment at 58.2 months in the ELEVATE-TN trial (ACA= 59.8%, ACA+OBIN= 67%), the ACAL doses were significantly underestimated. A more appropriate estimate for the equi-effective doses could be obtained if they were calculated from a 10-year extrapolation of the time to treatment discontinuation curves from the ELEVATE-TN trial. The ESC considered that the approach taken by the resubmission underestimated the use of ACA and hence favoured ACA+/-OBIN (resulted in a higher cost-minimised price for ACA+/-OBIN). The pre-PBAC response stated that the sponsor acknowledged a significant proportion of patients remained on treatment with ACA at this data cut, and that this may have led to an underestimation of mean time on treatment and total mean doses for the CMA.
- 6.47 No discounting was applied in the economic evaluation. The ESC noted discounting has an impact on the CMA because of the different treatment durations for ACA+/-OBIN versus VTX+OBIN, and applying discounting at 5% per annum would be consistent with the approach for the CMA for onasemnogene-abeparvovec versus nusinersen and risdiplam considered at the September 2021 PBAC meeting (paragraph 9.10, onasemnogene-abeparvovec, PSD, September 2021). The ESC noted due to the longer treatment duration for ACA+/-OBIN, without discounting, the cost-minimised price for ACA+/-OBIN is lower.
- 6.48 The resubmission considered additional costs and cost-offsets related to drug administration, adverse event management and tumour lysis syndrome prophylaxis.
- 6.49 The resubmission assumed 9 infusions would be required for OBIN in patients treated with regimens of either ACA+OBIN or VTX+OBIN. However, the actual number of infusions required in clinical practice would be lower given that not all patients would receive all infusions. In the ELEVATE-TN trial, the ACA+OBIN group on average, received 7.553 OBIN infusions. In the CLL-14 trial, the VTX+OBIN group received 7.355 OBIN infusions on average. If the trial data was utilised to estimate the number of infusions used in the CMA, this would result in a lower CMA price for ACA. For administration of OBIN, the resubmission only assumed that there would be an infusion administration cost based on MBS 13950 and did not consider the costs of a specialist visit and premedication costs associated with the infusion administration.

- 6.50 The resubmission considered cost-offsets from decreased management of Grade 3 or greater AEs in the CMA. The PBAC previously considered that the claim of superior comparative safety was not adequately supported by the data (paragraph 6.59, ACA, PSD, December 2022 PBAC intracycle meeting). Given no modifications were made to the previous safety data presented, a claim of a non-inferior safety profile would have been more appropriate and with that claim, AEs would not have been included in the CMA. The PSCR acknowledged the claim of superior safety, and thus calculation of associated cost offsets, were based on a MAIC analysis, which may be associated with uncertainty and hence that the sponsor would conservatively accept removal of cost offsets related to AEs from the CMA. The ESC considered the claim of superior safety was not supported and therefore it would be appropriate to remove the costs to manage AEs from the CMA. The pre-PBAC response stated that a clinical claim of non-inferior safety versus VTX+OBIN was pragmatically accepted.
- 6.51 The resubmission assumed that there would be a cost-offset from decreased utilisation of TLS prophylaxis associated with VTX treatment. This cost-offset was likely significantly overestimated due to the following:
- The calculated estimated cost per patient of \$3,784 to manage TLS was significantly greater than the \$1,329 (2023 adjusted value) per patient previously utilised in the July 2020 VTX submission (Table 8, VTX PSD, July 2020 PBAC meeting).
 - The resubmission assumed patients on ACA+OBIN treatment would not require TLS prophylaxis. This was unlikely as the ELEVATE-TN trial indicated that TLS was associated with the ACA+OBIN combination and the rate of TLS between ACA+OBIN versus VTX+OBIN was not statistically different ($p=1$).
- 6.52 The PSCR stated the cost of TLS prophylaxis was based on monitoring and healthcare resource requirements reported in the Venclexta[®] PI, indexed to the appropriate PBS and MBS costs and considered the cost of \$1,329 per patient noted in the evaluation to likely be a significant underestimate, especially considering the significant healthcare resource requirements required to prevent TLS (Gribben, 2020¹, Mato et al., 2018²). The PSCR stated TLS prophylaxis is not a requirement for ACA containing regimens (not specified in the Calquence[®] PI) and no such management was adopted in ELEVATE-TN for ACA or ACA+OBIN. The PSCR further noted the risk of TLS and the need for appropriate prophylactic management is recognised in the Venclexta[®] PI and was adopted in CLL-14 for patients treated with VTX+OBIN. The PSCR considered it likely that rates of TLS are comparable between ACA+OBIN and VTX+OBIN due to the different prophylaxis and management strategies adopted for patients treated with

¹ Gribben, J. G. 2020. Practical management of tumour lysis syndrome in venetoclax-treated patients with chronic lymphocytic leukaemia. *Br J Haematol*, 188, 844-851.

² Mato, A. R., Thompson, M., Allan, J. N., et al. 2018. Real-world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States. *Haematologica*, 103, 1511-1517.

VTX+OBIN in CLL-14. The ESC noted that TLS is generally due to the VTX component of VTX+OBIN and therefore it would be appropriate to apply the TLS prophylaxis cost to the VEN+OBIN arm only. The ESC considered the cost included in the July 2020 VTX submission (\$1,329, adjusted to 2023 value) to be a reasonable estimate for this cost. The pre-PBAC response stated that it considered that a cost of \$1,329 for TLS prophylaxis would be an acceptable estimate of the cost of TLS prophylaxis associated with cost of VTX, to be applied to the VTX+OBIN arm of the CMA only.

- 6.53 The resubmission did not present any final CMA results as the sponsor did not have access to the effective prices of VTX. The results of the economic evaluation as calculated during the evaluation using the published price for VTX are presented in Table 16.

Table 16: Results of the economic evaluation

Component	Proposed medicine			Comparator	
	ACA	ACA + OBIN		VTX +OBIN	
		ACA	OBIN	VTX	OBIN
Dose duration	1,473.18 days (48.4 months)	1,543.18 days (50.7 months)	163.4 days	288.1 days	144.05 days
Equi-effective dose (mg)	284,100	293,000	7,553.2	101,365.78	7,355
Number of scripts	50.73	52.32	7.553	9.67	7.355
Total cost of drug (DPMQ)	\$112,225.77 ^a	\$73,971.05 ^a	\$35,376.43	\$69,281.43	\$35,448.87
Total cost of drug (AEMP) ^b	\$109,545.36 ^a	\$72,457.11 ^a	\$35,209.96	\$67,736.88	\$34,313.00
Administration cost	n/a	n/a	\$1,027.80	n/a	\$1,027.80
Adverse event cost	\$589.66	\$1,566.50		\$4,300.94 ^c \$3,399.48 ^d	
Tumour lysis syndrome prophylaxis cost	n/a	n/a		\$3,784.20	
Total cost/per patient/course (DPMQ)	\$112,815.43	\$111,913.98		\$112,815.43 ^c \$111,913.98 ^d	
Total cost/per patient/course (AEMP) ^b	\$110,135.02	\$109,233.56		\$110,135.02 ^c \$109,233.56 ^d	
Total cost of drug using weighted ACA AEMP ^e	\$105,616.44 ^a	\$108,925.09	\$35,209.9 ^b	\$67,736.88 ^b	\$34,313.00 ^b
Total cost per patient/course using weighted ACA AEMP ^e	\$106,206.10	\$145,701.54		\$110,135.02 ^c \$109,233.56 ^d	
Weighted total cost of therapy ^e	\$110,155.64			\$110,044.87	
Difference in cost per patient/course versus VTX+OBIN ^f	-\$3,838.77	\$35,656.67		n/a	

Source: Table 3.3; Table 3.4; Attachment 3A; pp232 – 234 of the resubmission

ACA = acalabrutinib, AEMP = Approved Ex-Manufacturer Price, DPMQ = Dispensed Price for Maximum Quantity, OBIN = obinutuzumab, VTX = venetoclax.

^a No quantitative costs for ACA were presented in the resubmission. Values were calculated during the evaluation using the methodology stated in the resubmission.

^b The resubmission presented drug costs at the DPMQ/DPMA level. Values were recalculated at the AEMP level during the evaluation.

^c Compared to ACA monotherapy

^d Compared to ACA+OBIN

^e Weighted AEMP assumes 90/10% ACA+/-OBIN split. AEMP price calculated to be \$2,081.84 based on weighting of theoretical ACA prices in ACA therapy (\$2,159.29) and ACA+OBIN therapy (\$1,384.85).

^f Difference in cost per patient/course calculated as total cost per patient/course of ACA therapy using weighted ACA AEMP less equivalent total cost per patient/course of VTX+OBIN.

6.54 The results of key univariate sensitivity analyses conducted during the evaluation are summarised in Table 17. Variables tested in the univariate sensitivity analyses included:

- utilisation of ACA monotherapy versus ACA+OBIN. The proportion of use of ACA monotherapy vs ACA+OBIN was highly uncertain and not well justified. The ESC considered an 80% - 90% ACA monotherapy/10% - 20% ACA+OBIN split would be appropriate. The pre-PBAC response proposed a split of 85% ACA monotherapy/15% ACA+OBIN combination therapy.
- the costs for TLS prophylaxis and adverse events. As the claim of superior safety was not well supported, a sensitivity test that excluded AE costs, was performed.
- the duration of ACA+/-OBIN treatment. The PSCR and the pre-PBAC response noted that the PBAC had considered ZANU at its March 2023 meeting and indicated the sponsor would consider a CMA that assumed 67.02 scripts for ACA+/-OBIN if this was equivalent to the duration of treatment accepted for ZANU. The pre-PBAC response stated that as both ACA+/-OBIN are oral BTK inhibitors and that both are used until disease progression or unacceptable toxicity, it is likely the duration of treatment in this patient population would be comparable. The discounting and extrapolation of time on treatment were not able to be performed due to the structure of the cost-minimisation presented in the resubmission.

Table 17: Input parameters specific for sensitivity analyses conducted during the evaluation

Variable	Value for sensitivity analysis	Cost-minimising price	Relative to base case
Base case		\$2,081.84	
Relative utilisation of ACA+/-OBIN (base case= 90% /10%)	100% / 0%	\$2,159.29	3.7%
	80% / 20%	\$2,004.40	-3.7%
Costs associated with tumour lysis syndrome (base case assumed only VTX+OBIN at a cost of \$3,784.20 per patient)	TLS only considered for VTX+OBIN at a cost of \$1329 ^a per patient	\$2,033.60	-2.3%
	TLS considered for ACA+OBIN and VTX+OBIN at a cost of \$1329 ^a per patient	\$2,031.06	-2.4%
Cost of adverse events (base case: ACA+OBIN vs VTX+OBIN= \$1,566.50 VTX+OBIN vs ACA+OBIN= \$3,399.48 ACA vs VTX+OBIN= \$589.66 VTX+OBIN vs ACA= \$4,300.94)	Upper respiratory tract infection costs considered: ACA+OBIN vs VTX+OBIN: \$1,932.41 ACA vs VTX+OBIN: \$1,027.32	\$2,073.38	-0.4%
	No costs considered (non-inferiority in safety)	\$2,012.50	-3.3%
Premedication and specialist costs for OBIN administration (base case not considered for OBIN)	\$746.44 per patient per OBIN course in VTX+OBIN and ACA+OBIN	\$2,095.09	0.6%
Use of median treatment exposure (base case used mean treatment exposure: ACA= 48.4 months. ACA+OBIN= 50.7 months)	Median treatment exposure: ACA: 58.0 months ACA+OBIN: 58.1 months	\$1,702.17	-15.7%
Number of scripts with ACA+/-OBIN	Number of scripts = 67.02	\$1,579.18	-21.8%

Source: Attachment 3A of the resubmission, conducted during the evaluation and during preparation of the ESC Advice.

ACA = acalabrutinib, OBIN = obinutuzumab, TLS = tumour lysis syndrome; VTX = venetoclax, ZANU = zanubrutinib

^a Cost of TLS prophylaxis per patient based on July 2020 VTX submission (VTX PSD, July 2020 PBAC meeting), adjusted to 2023 value.

- 6.55 The PBAC noted the discounted treatment duration accepted for ZANU at the March 2023 meeting was 70.73 months (68.09 scripts) (paragraph 7.14, ZANU, PSD, March 2023 PBAC meeting). Based on this treatment duration, and adjusting for the dose intensity of ACA ($0.962 = 192.4/200$) and ACA+OBIN ($0.9425 = 188.5/200$) in the ELEVATE-TN trial³, that this would equate to 73.9 scripts for ACA when used as monotherapy ($0.962 \times 70.73 \times (365 \div 12 \div 28)$) and 72.4 scripts for ACA when used in combination with OBIN ($0.9425 \times 70.73 \times (365 \div 12 \div 28)$).

³ Attachment 2E: ELEVATE-TN 58.2-month CSR, Table 33, pp143-144. Mean relative dose intensity.

Acalabrutinib +/- obinutuzumab cost/patient/course**Table 18: Drug cost per patient for proposed and comparator drugs**

Drugs	Clinical study	Economic model ^a	Financial estimates ^b
ACA+OBIN			
ACA			
Cost per script	-	\$2,081.84 ^c	\$2,243.12
Adherence	Mean dose intensity (ELEVATE-TN): 94.2%	12.38 scripts per year (13.036 ^d scripts x 95.0% dose intensity) ^e	12.34 scripts per year (13.036 ^d scripts x 94.2% dose intensity)
Cost per year	-	\$25,773	\$27,680
Mean duration	50.7 months	50.7 months	50.7 months
Number of scripts per course	52.14	52.32	52.14
Cost per course	-	\$108,922	\$116,956
OBIN			
Cost per script	-	\$4,525.52	\$4,665.59
Compliance ^g	7.55 scripts/course ^f	7.55 scripts/course ^f	7.55 scripts/course ^f
Cost per course	-	\$34,168	\$35,221
Total cost per course	-	\$143,090	\$152,177
ACA monotherapy			
ACA			
Cost per script	-	\$2,081.84 ^c	\$2,243.12
Adherence	Mean dose intensity (ELEVATE-TN): 96.2%	12.58 scripts per year (13.036 ^d scripts x 96.5% dose intensity) ^e	12.54 scripts per year (13.036 ^d scripts x 96.2% dose intensity)
Cost per year	-	\$26,190	\$28,129
Mean duration	48.4 months	48.4 months	48.4 months
Number of scripts per course	50.58	50.73	50.58
Total cost per course	-	\$105,612	\$113,457
VTX+OBIN			
VTX			
Cost per script	-	Starter pack: \$1,645.3 Continuing pack: \$7,623.02	Starter pack: \$1,791.55 Continuing pack: \$7,784.30
Compliance	Mean treatment duration (CLL-14): 288.1 days	Starter pack: 1 script ^g Continuing pack: 8.67 scripts ^g	Starter pack: 1 script ^g Continuing pack: 8.67 scripts ^g
Cost per course	-	\$67,737	\$69,281
OBIN			
Cost per script (weighted price) ^h	-	\$4,525.52	\$4,665.09
Compliance	7.355 scripts/course	7.355 scripts (7.355 scripts x 100% dose intensity)	7.355 scripts (7.355 scripts x 100% dose intensity)
Cost per course	-	\$33,285	\$34,421
Total cost per course	-	\$101,022	\$103,702

Source: Compiled using the "3A – Acalabrutinib_1L CLL_CMA" and "4A – Acalabrutinib_1LCLL_Section4BIM" excel workbooks

ACA = acalabrutinib, OBIN = obinutuzumab, VTX = venetoclax

^a Cost per script calculated at the AEMP level^b Cost per script calculated based on estimated cost per script, using published DPMQ/DPMA^c AEMP for ACA as calculated during the evaluation using the methodology outlined in the resubmission and the published prices for VTX+OBIN^d Assuming 365 days/ year with each pack containing 56 tablets^e Based on the mean actual cumulative dose as reported in the ELEVATE-TN CSR^f Adjusted during the evaluation to reflect the trial-based utilisation however infusion costs were based on 9 administrations^g Based on the number of VTX scripts per course in the CLL-14 trial reported in Table 7 of the July 2020 Venetoclax PSD.^h Assuming 35.8% public utilisation and 64.2% private utilisation

Estimated PBS usage & financial implications

- 6.56 This resubmission was not considered by DUSC.
- 6.57 The resubmission used an epidemiological approach to estimate the utilisation and financial implications of listing ACA+/-OBIN in patients with previously untreated CLL/SLL. No justification was provided in the resubmission as to why an epidemiological approach was undertaken. Based on the non-inferior therapeutic conclusion, a market share approach would have been more appropriate. The PSCR stated an epidemiological approach was adopted for consistency with previous submissions for ACA+/-OBIN as well as the approach accepted by the PBAC for VTX+OBIN in July 2020 (venetoclax July 2020 PSD) in previously untreated CLL. The PBAC noted the zanubrutinib submission for treatment naïve CLL used a market share approach (paragraph 7.16, ZANU, PSD, March 2023 PBAC meeting).
- 6.58 The key inputs for financial estimates are presented in Table 19.

Table 19: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incident CLL patients	2024: 2,591 2025: 2,629 2026: 2,667 2027: 2,704 2028: 2,741 2029: 2,777	Incidence of 9.4/100,000 (crude rate; 2022 (AIHW estimate) applied to ABS population projections.	The estimated crude incidence rate was updated from 8.6/100,000 in the November 2022 resubmission to reflect advice from the PBAC. The AIHW data also suggests a trend towards increasing incidence over time.
Patients initiating treatment within first year of diagnosis	30%	Table 8 VTX July 2020 submission/PSD (sponsor assumption).	Unchanged since the November 2022 resubmission. No additional justification provided.
Patients initiating treatment within 5 years	30%. Assumed 7.5% each in years 2, 3, 4 and 5 following CLL diagnosis	Table 8 VTX July 2020 submission/PSD (sponsor assumption).	Unchanged since the November 2022 resubmission. No additional justification provided.
Treatment utilisation			
Estimated utilisation split between ACA+OBIN and ACA monotherapy	ACA+OBIN: 10% ACA mono: 90%	Sponsor's assumption	The assumption was based on limited evidence. Although ACA has a better safety profile, it is less effective compared to ACA+OBIN. The proportion of patients who would be better candidates for ACA+OBIN relative to ACA monotherapy is yet to be determined. The ESC considered the estimated utilisation could be in the range of 80-90% ACA monotherapy and 10-20% ACA+OBIN. The pre-PBAC response proposed a split of 85% ACA monotherapy/15% ACA+OBIN combination therapy.
Current market share of VTX+OBIN	90%	Table 8 VTX July 2020 submission.	Unchanged since the November 2022 resubmission. No additional justification provided. This was likely an overestimation. No substitution of CHL+OBIN was considered.
Uptake/replacement rate of ACA + OBIN for VTX + OBIN	2024: 30% 2025: 40% 2026: 50% 2027: 50% 2028: 50%	Sponsor's assumption	ZANU was considered at the March 2023 PBAC meeting in patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy. It is possible that the market share of ACA could

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Data	Value	Source	Comment
	2029: 50%		be significantly overestimated given ZANU received a positive PBAC recommendation.
Duration of ACA treatment	ACA mono: 48.4 months ACA+OBIN: 50.7 months	Mean duration of treatment reported from the 58.2-month data-cut from the ELEVATE-TN trial.	The ESC noted the mean was censored with the majority of patients remaining on ACA at study end (ACA= 59.8%, ACA+OBIN= 67%). On this basis the ESC considered the treatment duration was underestimated.
Number of OBIN scripts per patient when treated with ACA+OBIN	7.55	Based on planned number of doses (8) from the ELEVATE-TN trial and adjusted by the observed dose intensity (94.2%).	It may not be reasonable to assume use in Australian clinical practice will be equivalent to use in the ELEVATE-TN trial.
Number of OBIN scripts per patient when treated with VTX+OBIN	7.35	Based on the number of OBIN scripts per course in the CLL-14 trial reported in Table 7 of the July 2020 VTX PSD.	Unchanged since the November 2022 resubmission. No additional justification provided.
Number of VTX scripts per patient when treated with VTX+OBIN	Initial: 1 Continuing: 8.67	Based on the number of VTX scripts per course in the CLL-14 trial reported in Table 7 of the July 2020 VTX PSD.	Unchanged since the November 2022 resubmission. No additional justification provided.

Source: "4A – Acalabrutinib_1LCLL_Section4BIM" excel workbook

ACA = acalabrutinib, OBIN = obinutuzumab, PSD = public summary document, VTX = venetoclax; ZANU = zanubrutinib.

6.59 Based on PBS/RPBS data, from January 2022 to December 2022 there were 471 initiating VTX scripts, 4,048 VTX continuing scripts, and 3,608 OBIN scripts. The resubmission estimated that the number of replaced scripts in 2024 would be 412 initiating VTX scripts, 3,570 VTX continuing scripts, and 3,026 OBIN scripts. Given the assumption of ACA+/-OBIN having 30% market share in 2024, the implied total number of scripts for VTX+OBIN would be 1,373 (412/30%) initiating VTX scripts, 11,900 (3,570/30%) VTX continuing scripts, and 10,087 (2,036/30%) OBIN scripts. The large difference in the actual number of VTX and OBIN scripts in 2022 and the projected number in 2024 (of which 30% are replaced by ACA+/-OBIN) suggested that the epidemiological approach used substantially overestimated use of VTX+OBIN, and hence similarly overestimated use of ACA+/-OBIN. The PSCR noted that the PBAC had advised that the criterion that patients be 'inappropriate for fludarabine-based chemoimmunotherapy' should be removed from the existing VTX+OBIN restriction (December 2022 PBAC meeting outcomes) and on this basis considered a market share approach was unlikely to lead to accurate estimates of the financial impact of ACA+/-OBIN listing. The ESC considered given the low use of fludarabine that the restriction change would have minimal impact on the use of VTX+OBIN. The pre-PBAC response noted this and provided the results of the financial estimates (at published prices), assuming 65% of patients are inappropriate for 'inappropriate for fludarabine-based chemoimmunotherapy'.

6.60 The estimated financial implications are presented in Table 20. The estimated financial implications use the ACA price calculated in the CMA (\$2,081.84 AEMP/ \$2,243.12

DPMQ). The financial implications presented in the resubmission used the proposed published price (\$8,219.02 DPMQ). The proposed published price for ACA being substantially higher than the equivalent published prices for VEN+OBIN resulted in an increase in PBS/RPBS spend in the resubmission’s estimates.

Table 20: Estimated financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of ACA+/-OBIN						
Number of ACA scripts dispensed	█ ¹	█ ²	█ ³	█ ³	█ ⁴	█ ⁴
Number of OBIN scripts dispensed	█ ⁵	█ ⁵	█ ⁶	█	█ ⁶	█ ⁶
Estimated financial implications of ACA+/-OBIN						
ACA cost to PBS/RPBS less copayments (\$)	█ ⁷	█ ⁸	█ ⁹	█ ¹⁰	█ ¹¹	█ ¹²
OBIN cost to PBS/RPBS less copayments (\$)	█ ¹³	█ ¹³	█ ¹³	█ ¹³	█ ¹³	█ ¹³
Total cost to PBS/RPBS less copayments (\$)	█ ⁷	█ ⁸	█ ⁹	█ ¹⁰	█ ¹¹	█ ¹²
Estimated financial implications (saving) for VTX+OBIN						
VTX save to PBS/RPBS less copayments (\$)	█ ⁸	█ ¹⁴	█ ⁹	█ ⁹	█ ¹⁵	█ ¹⁵
OBIN save to PBS/RPBS less copayments (\$)	█ ⁷	█ ⁷	█ ⁸	█ ⁸	█ ⁸	█ ⁸
Total save to PBS/RPBS less copayments (\$)	█ ⁹	█ ¹⁵	█ ¹¹	█ ¹¹	█ ¹¹	█ ¹¹
Net financial implications						
Net cost to PBS/RPBS (\$)	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹³	█ ¹³
Net cost to MBS/Services Australia/other (\$)	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹⁶
Net cost to PBS/RPBS/MBS/Services Australia (\$)	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹⁶	█ ¹³	█ ¹³

Source: Table 4.24, p261 of the resubmission, adjusted during the evaluation and recalculated based on a published price of \$2,243.12 per script for acalabrutinib (calculated as a cost-minimised price based on the published prices of the comparators)

ACA = acalabrutinib, OBIN = obinutuzumab, VTX = venetoclax

The redacted values correspond to the following ranges:

- ¹ 5,000 to < 10,000
- ² 10,000 to < 20,000
- ³ 20,000 to < 30,000
- ⁴ 30,000 to < 40,000
- ⁵ < 500
- ⁶ 500 to < 5,000
- ⁷ \$10 million to < \$20 million
- ⁸ \$20 million to < \$30 million
- ⁹ \$40 million to < \$50 million
- ¹⁰ \$60 million to < \$70 million
- ¹¹ \$70 million to < \$80 million
- ¹² \$80 million to < \$90 million
- ¹³ \$0 to < \$10 million
- ¹⁴ \$30 million to < \$40 million
- ¹⁵ \$50 million to < \$60 million
- ¹⁶ net cost saving

6.61 The total net financial impact on the PBS/RPBS/MBS of listing ACA+/-OBIN was estimated to be net cost saving in year 1 and \$0 to < \$10 million in year 6, using the calculated CMA price for ACA and the published DPMQ/DPMA prices for VEN and

OBIN. The ESC noted the cost savings in the initial years and the additional costs in later years reflect the different treatment durations and hence distribution of costs over time. The average treatment duration with VEN+OBIN is approximately 10 months and so all of the costs accrue in the year in which treatment is initiated, whereas the average treatment duration with ACA+/-OBIN is approximately 50 months and so the costs accrue over 4.2 years.

- 6.62 The duration of treatment with ACA+/-OBIN was informed by the duration of treatment reported from the 58.2-month data-cut from ELEVATE-TN. The mean treatment durations for ACA+OBIN and ACA monotherapy were 50.7 months and 48.4 months respectively. An adjustment for dose intensity was also applied by reducing the number of scripts required to align with observed dose intensity in the ELEVATE-TN trial (94.2% for ACA+OBIN and 96.2% for ACA).
- 6.63 The duration was likely to be significantly underestimated as the majority of patients remained on treatment at the end of the trial follow-up. The PSCR presented revised financial estimates assuming 67.02 ACA scripts per patient and a DPMQ per script of \$8,219.02. The PSCR noted that given the proposed listing is on a cost-minimisation basis, when effective prices are used, the listing of ACA+/-OBIN is expected to be cost-neutral to the PBS. The ESC noted the different treatment durations for ACA+/-OBIN and VEN+OBIN will initially result in a cost savings with additional costs in later years. The pre-PBAC response presented a revised version of the financial estimates from the PSCR. The revised estimates presented were based on a treatment duration of 67.02 scripts per patient, as well as a reduction in patient numbers of approximately 35% to account for the comment by the ESC, that patient numbers were considered to be underestimated (as per paragraph 6.59).
- 6.64 ZANU, a near-market comparator to ACA, was recommended at the March 2023 PBAC meeting for the treatment of patients with previously untreated CLL/SLL. The availability of an alternative BTKi (ZANU) may significantly affect the uptake of ACA. The PSCR and the pre-PBAC response stated that as a consequence of the positive recommendation for ZANU, it is expected that the total BTKi share would be similar, but market shares for each of ZANU and ACA+/-OBIN would be estimated as half of the shares in the resubmission.
- 6.65 At the time of PBAC consideration, no oral therapy was available on the PBS for patients with previously untreated CLL/SLL. Should ACA be listed as the first available oral therapy, the ESC considered there is potential for use of ACA beyond the population specified as ACA may be used earlier in treatment given it is an oral therapy. The PSCR stated that the sponsor is open to working with the Department to ensure the appropriate wording in the PBS restriction for ACA+/-OBIN to limit treatment to the intended population and noted the Secretariat proposed changes to include reference to the iwCLL guidelines in the restriction.

Financial Management – Risk Sharing Arrangements

- 6.66 The resubmission stated that the sponsor was willing to work with the Department to implement appropriate Risk Share Arrangements (RSA) such that the listing of ACA+/- OBIN in this patient population remains cost-neutral.

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

7 PBAC Outcome

- 7.1 The PBAC recommended extending the listing of acalabrutinib (ACA) to include the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). The PBAC considered the nominated comparator of venetoclax plus obinutuzumab (VTX+OBIN) was appropriate. The PBAC's consideration was based on, among other matters, its assessment as described above, that the cost-effectiveness of ACA as monotherapy (assuming 85% of use) or in combination with obinutuzumab (OBIN) (assuming 15% of use) would be acceptable if it were cost-minimised to VTX+OBIN, and zanubrutinib (ZANU) if PBS listed for previously untreated patients. The PBAC considered a Risk Sharing Arrangement (RSA) would be required to manage the risks of the duration of treatment with ACA being longer than modelled and earlier use in patients not meeting the International Workshop on CLL (iwCLL) criteria for initiating treatment. The PBAC advised that ACA should join the ZANU RSA should ZANU have progressed to PBS listing for previously untreated CLL/SLL.
- 7.2 The PBAC noted the input from Rare Cancers Australia describing how the availability of an oral treatment could give back more time to patients, and lead to improved quality of life.
- 7.3 The PBAC considered that the nominated main comparator of VTX+OBIN was appropriate. The PBAC noted that ZANU had received a recommendation for listing at the March 2023 PBAC meeting and that the resubmission had appropriately nominated ZANU as a near market comparator.
- 7.4 The PBAC noted this was the fourth submission for ACA for this indication, and that this resubmission was based on the ELEVATE-TN trial (ACA+/-OBIN vs chlorambucil [CHL]+OBIN) and the CLL-14 trial (VTX+OBIN vs OBIN+CHL), which it had considered previously. The PBAC noted that the resubmission had also presented data from the SEQUOIA trial for ZANU (vs bendamustine + rituximab [BEND+RIT]).
- 7.5 The PBAC noted there was a small but significant improvement in the progression free survival (PFS) rates for ACA+OBIN compared to ACA monotherapy in the ELEVATE-TN trial (93% versus 87% at 24 months and 84% versus 72% at 60 months), but no difference in overall survival (OS). The PBAC noted that, reflecting the indolent nature of CLL, OS data from the ELEVATE-TN trial was immature with median OS not having been reached.

- 7.6 The PBAC noted that the resubmission had presented a Matching Adjusted Indirect Comparison (MAIC) anchored to the common comparator of CHL+OBIN, using updated data from ELEVATE-TN with a median follow-up of 58.2 months and CLL-14 with a median follow-up of 52.4 months. The PBAC noted that the resubmission had not provided baseline characteristics before and after matching, and as such, it was not able to assess the reliability of the MAIC.
- 7.7 The PBAC noted that based on the ELEVATE-TN trial there was a statistically significant 89% reduction in the risk of progression or death for ACA+OBIN compared to CHL+OBIN (HR: 0.11 [95% CI: 0.07, 0.16]) and a 79% reduction for ACA monotherapy compared to CHL+OBIN (HR: 0.21 [95% CI: 0.15, 0.30]). In the CLL-14 trial the reduction in the risk of progression or death for VEN+OBIN compared with CHL+OBIN was 67% (HR: 0.33 [95% CI: 0.25, 0.45]). The PBAC considered, even though the MAIC was unreliable, based on the PFS results from the individual trials together with its previous acceptance of a claim of non-inferior effectiveness for ZANU versus ACA in the relapsed/refractory setting and for ZANU versus VEN+OBIN in the treatment naïve setting, the claim that ACA+/-OBIN is non-inferior in effectiveness to VTX+OBIN was likely reasonable.
- 7.8 The PBAC noted the safety comparisons for ACA+/-OBIN versus VEN+OBIN were the same as presented in the December 2022 submission and recalled that it had considered a claim of superior safety was not adequately supported. The PBAC noted that a claim of non-inferior safety for ACA+/-OBIN compared with VEN+OBIN was accepted in the pre-PBAC response and considered this claim was reasonable.
- 7.9 The PBAC recalled that it had recommended ZANU for listing at its March 2023 meeting and noted that the resubmission presented an unanchored unmatched (naïve) comparison of ACA+/-OBIN and ZANU based on ELEVATE-TN (median follow-up of 28.4 months) and SEQUOIA (median follow-up of 30.5 months). The PBAC noted the control arms in the two trials differed, OBIN+CHL in ELEVATE-TN and BEND+RIT in SEQUOIA, however considered based on a numerical comparison of the trial results that ACA+/-OBIN is likely to have PFS and OS of a similar magnitude to ZANU, noting that the OS data is immature. Based on this, and its previous acceptance of a claim of non-inferior effectiveness for ZANU vs ACA in the relapsed/refractory setting, the PBAC considered a claim of non-inferior comparative effectiveness of ACA+/- OBIN compared to ZANU was likely reasonable. The PBAC similarly considered that a claim of non-inferior comparative safety of ACA+/- OBIN compared to ZANU was likely reasonable.
- 7.10 The PBAC noted that the resubmission presented a cost-minimisation approach (CMA) of ACA+/-OBIN compared to VTX+OBIN. The PBAC noted this was in line with its advice from the December 2022 meeting and considered this was appropriate and consistent with the claim of non-inferior efficacy and safety.

- 7.11 The PBAC noted that while the resubmission had included a cost differential for the treatment of adverse events, it was agreed in the pre-PBAC response to exclude these costs. The PBAC considered this was appropriate.
- 7.12 The PBAC noted a cost-offset for tumour lysis syndrome (TLS) prophylaxis of \$3,784 for patients receiving VTX was included in the CMA. The PBAC considered that a cost of \$1,329 for TLS prophylaxis was appropriate noting that this was considered acceptable in the pre-PBAC response and was the same as included in the CMA for ZANU versus VEN+OBIN.
- 7.13 The PBAC noted that the truncated mean treatment duration for ACA in the ELEVATE-TN trial was 48.4 months when ACA was used as monotherapy and 50.7 months when ACA was used in combination with OBIN. However, given that a significant proportion of patients remained on treatment at the end of the 58.2-month follow-up period (60% and 67%, respectively), the mean ACA duration was substantially underestimated. The PBAC recalled in its consideration of ZANU for previously untreated patients at the March 2023 PBAC meeting that a treatment duration of 70.73 months, using a discount rate of 5% per annum, was accepted (paragraph 6.67, ZANU, PSD, March 2023 PBAC meeting). The PBAC considered this is a reasonable estimate of the likely mean treatment duration for ACA+/-OBIN.
- 7.14 The PBAC noted the CMA was undertaken assuming a relative uptake ratio of 90%/10% for ACA monotherapy/ACA+OBIN. The PBAC noted that the ESC had suggested a relative ratio of between 90%/10% and 80%/20% and that in the pre-PBAC response a ratio of 85%/15% was pragmatically agreed to for determining a weighted price for ACA. The PBAC considered the relative uptake ratio to be uncertain, but a relative ratio of 85%/15% for ACA monotherapy/ACA+OBIN use for the purposes of determining a weighted price for ACA, to be reasonable.
- 7.15 Consistent with the equi-effective doses for ZANU and VEN+OBIN (paragraph 7.14, ZANU, PSD, March 2023 PBAC meeting), the PBAC considered the equi-effective doses were:
- One initial and 8.67 continuing VEN scripts plus 7.355 OBIN scripts
 - 70.73 months of ZANU treatment at a dose of 304 mg daily (68.09 scripts)
 - 70.73 months of ACA monotherapy at a dose of 192.4 mg daily (73.9 ACA scripts) (85% of use) and 70.73 months of ACA at a dose of 188.5 mg daily (72.4 ACA scripts) plus 7.553 scripts of OBIN (15% of use).
- 7.16 The PBAC considered for the purpose of Section 101(3B) of the *National Health Act 1953*, that ACA+/-OBIN was an alternative therapy to ZANU, and that ACA+/-OBIN does not provide a significant improvement in efficacy and/or reduction of toxicity over ZANU. The PBAC advised that the price of ACA+/-OBIN should therefore be not higher than the price of ZANU, based on the above equi-effective doses, should ZANU be PBS listed for previously untreated patients.

- 7.17 The PBAC noted the resubmission used an epidemiological approach to derive the expected utilisation and cost to the PBS/RPBS over 6 years. The PBAC noted that this approach derived an implied number of scripts for VTX in 2024 that was more than three times the utilisation of VTX in 2022, and that this was implausible. The PBAC considered that the epidemiological approach overestimated the expected utilisation and that it would have been appropriate to have used a market share approach to define the market using PBS data for VTX and OBIN.
- 7.18 The PBAC noted that if ZANU is listed for previously untreated patients, the listing of ACA+/-OBIN will be cost neutral regardless of the uptake given listing on a cost minimisation basis. The pre-PBAC response suggested the uptake for ACA+/-OBIN and ZANU would be approximately the same with each obtaining 50% of the first-line BTK inhibitors market. The PBAC considered the uptake of each agent to be uncertain, although noted 50% was plausible.
- 7.19 The PBAC noted if ZANU is not PBS listed for previously untreated patients and hence ACA+/-OBIN replaces VTX+OBIN that there would be a cost saving in the initial years due to the cost for ACA+/-OBIN accruing over a longer period of time than the cost-offsets for VTX+OBIN however, this would reverse to a net cost in later years. The PBAC considered the financial estimates provided in the resubmission, including in the PSCR and pre-PBAC response, were unreliable for the reason outlined in paragraph 7.17. The PBAC considered the financial estimates should be calculated using a market share approach as outlined in the PSD for the consideration of ZANU (paragraph 7.16, ZANU, PSD, March 2023 PBAC meeting). Specifically, recent VTX and OBIN prescription data should be used to define the market, no market growth should be assumed, the uptake for ACA+/-OBIN should be 40% and the treatment duration for ACA+/-OBIN should be as used in the CMA with discounting removed.
- 7.20 The PBAC noted that the sponsor had proposed a RSA, and considered that this was appropriate to manage the risk of (i) the treatment duration being longer with the additional use potentially not being cost-effective and (ii) earlier use in patients not meeting the iwCLL criteria for initiating treatment with such use potentially not being cost-effective. The PBAC considered that should ZANU be PBS-listed that it would be appropriate for ACA to join the ZANU RSA, since both are time unlimited BTK inhibitors. The PBAC considered that should ZANU not be PBS-listed that it may not be appropriate to add ACA+/-OBIN to the existing RSA for VTX as the identified risks regarding ACA+/-OBIN use do not apply. In this case the PBAC considered the financial caps should be based on revised financial estimates as outlined in paragraph 7.19.
- 7.21 The PBAC noted that flow-on restriction changes would be required for OBIN.
- 7.22 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ACA+/-OBIN is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over VTX+OBIN, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health*

(Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.

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

Outcome:

Recommended

8 Recommended listing

8.1 Add indication as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB 100 mg, tablet	NEW	1	56	5	Calquence
		Max.qty (packs) multiplier = 2 Repeat increases: nil			
Restriction Summary] / Treatment of Concept:					
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities				
	Administrative advice: No increase in the maximum number of repeats may be authorised.				
	Administrative advice: Special Pricing Arrangements apply.				
	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: 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.				
	Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Treatment Phase: First line drug treatment of this indication - as monotherapy				
	Clinical criteria:				
	The condition must be untreated with acalabrutinib at the time of the first dose of this drug; or				

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	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 the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.
	Treatment criteria:
	Patient must be undergoing initial treatment with this drug – this is the first PBS prescription for this drug; or
	Patient must be undergoing continuing treatment with this drug – the condition has not progressed whilst the patient has actively been on this drug

MEDICINAL PRODUCT medicinal product pack	PBS code	item	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ACALABRUTINIB 100 mg, tablet	NEW		1	56	6	Calquence
			Max.qty (packs) multiplier = 2 Repeat increases: nil			

Restriction Summary / Treatment of Concept:

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	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: 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.
	Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: First line drug treatment of this indication – in combination with obinutuzumab

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	Clinical criteria:
	The condition must be untreated with acalabrutinib 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 a monotherapy for 1 Cycle with treatment in combination with obinutuzumab from Cycle 2 to 7 (refer to Product information for timing of obinutuzumab and acalabrutinib doses) after which treatment must be monotherapy
	Treatment criteria:
	Patient must be undergoing initial treatment with this drug – this is the first PBS prescription for this drug; or
	Patient must be undergoing continuing treatment with this drug – the condition has not progressed whilst the patient has actively been on this drug

8.2 Flow-on changes to OBIN as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max amount	No. of Rpts	Available brands
OBINUTUZUMAB obinutuzumab 1 g/40 mL injection, 40 mL vial	NEW	1000 mg	5	GAZYVA
Restriction Summary / Treatment of Concept:				
Concept ID	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals)			
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined			

	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
	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.
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: For combination use with acalabrutinib from treatment cycles 2 to 7 inclusive in first-line therapy
	Clinical criteria:
	The condition must be untreated
	AND
	Clinical criteria:
	The treatment must be in combination with PBS-subsidised acalabrutinib (refer to Product Information for timing of obinutuzumab and acalabrutinib doses)

The restriction and flow-on changes may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.