

**7.01 ACALABRUTINIB,  
Capsule 100 mg,  
Calquence<sup>®</sup>,  
AstraZeneca Pty Ltd.**

**1 Purpose of resubmission**

- 1.1 The standard re-entry resubmission requested an Authority Required General Schedule listing of acalabrutinib, for use in combination with obinutuzumab, for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), who are considered unsuitable for treatment with fludarabine-based chemoimmunotherapy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus venetoclax + obinutuzumab. Listing was requested for acalabrutinib + obinutuzumab only (the July 2020 submission requested listing of acalabrutinib for use as monotherapy or in combination with obinutuzumab; the November 2021 resubmission requested listing of acalabrutinib monotherapy only).

**Table 1: Key components of the clinical issue addressed in the resubmission**

Component	July 2020 submission	November 2021 resubmission	Current resubmission
Population	<p>Patients with previously untreated CLL or SLL considered unsuitable for treatment with a purine analogue, an ECOG <math>\leq 2</math>, and meeting at least one of the following criteria:</p> <ul style="list-style-type: none"> <li>- Age <math>\geq 65</math> years;</li> <li>- Age 18 - 65 years with a CIRS score <math>\geq 6</math> or a CrCl <math>&lt; 70</math> mL/min;</li> <li>- 17p deletion.</li> </ul>	<p>Patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy, and who meet the following criteria:</p> <ul style="list-style-type: none"> <li>- CIRS score <math>&gt; 6</math>; AND</li> <li>- Renal impairment (CrCl <math>\geq 30</math> and <math>&lt; 70</math> ml/min); AND/OR bulky disease (lymph node(s) <math>\geq 5</math>cm); OR moderate or high risk of TLS; AND</li> <li>- Unsuitable for venetoclax + obinutuzumab as unable to comply with the monitoring required for TLS prophylaxis and dose escalation requirements.</li> </ul> <p>Patients who initiate treatment with venetoclax + obinutuzumab but develop intolerance of a severity necessitating permanent treatment withdrawal prior to completion of the course and before disease progression (pre-progression discontinuation).</p>	<p>Patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy, a CrCl <math>\geq 30</math> mL/min, and who meet one of the following criteria:</p> <ul style="list-style-type: none"> <li>- CIRS score <math>&gt; 6</math>;</li> <li>- CrCl <math>&lt; 70</math> mL/min.</li> </ul>
Intervention	<ul style="list-style-type: none"> <li>- Acalabrutinib monotherapy.</li> <li>- Acalabrutinib + obinutuzumab.</li> </ul>	<ul style="list-style-type: none"> <li>- Acalabrutinib monotherapy: oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity.</li> </ul>	<ul style="list-style-type: none"> <li>- Acalabrutinib + obinutuzumab: oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity plus</li> </ul>

Component	July 2020 submission	November 2021 resubmission	Current resubmission
			intravenous obinutuzumab for six cycles.
Comparator	- Chlorambucil + obinutuzumab - Ibrutinib monotherapy (patients with 17p deletion) - Venetoclax + obinutuzumab (near-market comparator)	- Chlorambucil + obinutuzumab: oral chlorambucil for six cycles + intravenous obinutuzumab for six cycles.	- Venetoclax + obinutuzumab: oral venetoclax 5-week dose ramp-up followed by 400 mg daily for twelve cycles + intravenous obinutuzumab for six cycles.
Outcomes	Progression-free survival, overall response rate, overall survival, safety.	Progression-free survival, overall response rate, time to next treatment, overall survival, safety.	Progression-free survival, overall response rate, time to next treatment, overall survival, safety.
Clinical claim	In patients with previously untreated CLL considered unsuitable for treatment with a purine analogue: - Acalabrutinib + obinutuzumab is superior in terms of efficacy, and no worse in terms of safety compared to chlorambucil + obinutuzumab. - Acalabrutinib monotherapy is superior in terms of efficacy and safety compared to chlorambucil plus obinutuzumab. - Acalabrutinib + obinutuzumab is non-inferior in terms of PFS and OS but has a higher ORR compared to venetoclax + obinutuzumab and is non-inferior in terms of safety compared to venetoclax + obinutuzumab. - Acalabrutinib monotherapy is non-inferior in terms of efficacy, and superior in terms of safety compared to venetoclax + obinutuzumab.  In patients with previously untreated CLL with 17p deletion considered unsuitable for treatment with a purine analogue: - Acalabrutinib monotherapy is non-inferior in terms of efficacy, and superior in terms of safety compared to ibrutinib monotherapy.	In patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, or who become intolerant to venetoclax + obinutuzumab, acalabrutinib is superior in terms of efficacy and safety compared to chlorambucil + obinutuzumab.	In patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy, acalabrutinib + obinutuzumab is superior to venetoclax + obinutuzumab in terms of efficacy and safety.

Source: Table 1.1.1 of the July 2020 acalabrutinib commentary document; Table 1.1.1 of the November 2021 acalabrutinib commentary document; Table 1.2 of the resubmission.

CLL = chronic lymphocytic leukaemia, CIRS = Cumulative Illness Rating Scale, CrCl = creatinine clearance, SLL = small lymphocytic leukaemia, TLS = tumour lysis syndrome

## 2 Background

### Registration status

2.1 Acalabrutinib was registered on the ARTG on 21 November 2019 for the treatment of patients with CLL/SLL.

## Previous PBAC consideration

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Proposed population	The PBAC noted that the resubmission had proposed listing in a narrower population than the original submission. The PBAC considered that there was a clinical rationale for the narrower listing, but that the clinical need could also be addressed with a broader listing extended to the population who are unsuitable for fludarabine-based chemotherapy (para 7.5, November 2021 PSD).	Addressed. The resubmission requested listing for a broader patient population (patients who are unsuitable for treatment with fludarabine-based chemoimmunotherapy).
Comparator	Based on the proposed restriction, the PBAC considered venetoclax + obinutuzumab to be a relevant comparator (para 7.6, November 2021 PSD).	Addressed. Venetoclax + obinutuzumab was nominated as the main comparator in the resubmission.
Clinical place in therapy	The PBAC noted that although a post hoc analysis of the pivotal clinical trial (ELEVATE-TN) demonstrated that acalabrutinib + obinutuzumab was superior to acalabrutinib monotherapy on the basis of independent review committee-assessed progression free survival (HR = 0.49 [95% CI: 0.26, 0.95]), combination therapy was associated with substantial additional toxicity. Overall, the Committee considered it likely that acalabrutinib monotherapy would be used in the majority of patients unsuitable for treatment with a purine analogue given the additional toxicity of combination therapy together with the general frailty of the patient population (para 7.3, July 2020 PSD).	Listing was only requested for combination therapy with acalabrutinib + obinutuzumab.
Clinical effectiveness	The PBAC considered that the efficacy and safety matching adjusted indirect comparisons (MAICs) between both acalabrutinib monotherapy and acalabrutinib + obinutuzumab and venetoclax + obinutuzumab were highly uncertain. The PBAC noted the heterogeneity between the ELEVATE-TN and CLL-14 trials which resulted in poor overlap between the trial populations and small effective sample sizes for the MAICs and considered that it was unclear whether all relevant prognostic and effect modifier variables had been identified. Overall, the PBAC considered that the efficacy and safety clinical claims based on the MAICs could not be supported (para 7.9, July 2020 PSD).	The resubmission presented updated MAICs for acalabrutinib + obinutuzumab and acalabrutinib monotherapy versus venetoclax + obinutuzumab. Matching was limited to selected treatment effect modifier variables.
Economic analysis	The PBAC considered that it would be inappropriate to model an overall survival gain in the economic evaluation as the data remained immature and there may not be a difference over the longer term given subsequent lines of effective therapy are available (para 7.8, November 2021 PSD).	The economic model incorporated an overall survival gain associated with acalabrutinib + obinutuzumab compared to venetoclax + obinutuzumab, based on updated clinical data presented in the resubmission.
Economic analysis	A 10-year time horizon would be more reasonable than a 15-year horizon, as it would be consistent with previous decisions in the first-line CLL/SLL setting, the proposed PBS population was likely to be somewhat more frail than the general fludarabine-unsuitable first-line population, and given that a longer extrapolation would be subject to considerable uncertainty (para 7.10, November 2021 PSD).	The resubmission base case assumed a 15-year time horizon.

Component	Matter of concern	How the resubmission addresses it
Economic analysis	The PBAC noted that a key limitation of the model structure was that the assumed progressed disease health state cost and utility may not adequately reflect the cost and quality of life experienced by patients with CLL/SLL over time, given multiple lines of subsequent therapy, and periods of disease remission. The PBAC also noted underlying uncertainty with subsequent treatment costs and utilities as they were not informed by ELEVATE-TN data (para 7.10, November 2021 PSD).	The resubmission model structure, health state utilities, and health state costs were updated to align with the model included in the July 2020 venetoclax resubmission.
Economic analysis	The extrapolated progression-free survival curve was subject to substantial uncertainty (para 7.10, November 2021 PSD).	As in the November 2021 resubmission, progression-free survival for acalabrutinib + obinutuzumab was based on extrapolated ELEVATE-TN data for the September 2020 data cut.
Economic analysis	The use of a 48-month treatment cap to achieve cost-effectiveness was not a robust approach, and that the ICER would be much higher if patient numbers used to inform the caps were lower than estimated (para 7.10, November 2021 PSD). The PBAC also noted the ESC's concerns about the proposed risk-sharing arrangement, and the sponsor's proposed alternative arrangements, but considered that it was unclear what scenario would ensure that the modelled cost-effectiveness would be realised in practice (para 7.12, November 2021 PSD).	The resubmission proposed an RSA in which the cost of acalabrutinib for each patient is capped at 60 months of treatment, with the financial estimates presented in the resubmission forming the basis for the RSA caps. The pre-PBAC response withdrew this proposal.
Financial estimates	The PBAC considered that the estimated cost to the PBS/RPBS of listing acalabrutinib and the estimated changes in use of other medicines were highly uncertain (para 7.12, November 2021 PSD).	The resubmission provided updated financial estimates based on a mixed epidemiological/market share approach, with cost offsets associated with substitution for venetoclax + obinutuzumab treatment, and changes in later-line therapy utilisation.

Source: July 2020 and November 2021 acalabrutinib Public Summary Documents.  
PSD = Public Summary Document

### 3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack	PBS code	item	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<i>ACALABRUTINIB</i>						
<del>ACALABRUTINIB, Treatment of patients with previously untreated CLL or SLL, 100 mg capsule, oral administration 100 mg, capsule</del>	<i>NEW</i>		1	56	<del>26</del>	Calquence
			<i>Max.qty (packs) multiplier = 2</i>			
			<i>Repeat increases: nil</i>			
<b>Restriction Summary / Treatment of Concept:</b>						

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<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative advice:</b> Special Pricing Arrangements apply.
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Condition:</b> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Indication:</b> <del>Patients with previously untreated CLL/SLL</del> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Treatment Phase:</b> Initial treatment (treatment cycles 1 to 3 inclusive) in first-line therapy
<b>Clinical criteria:</b>
The condition must be <del>previously</del> untreated,
<b>AND</b>
<b>Clinical criteria:</b>
<del>Patient must be considered unsuitable for fludarabine-based chemoimmunotherapy,</del>
<b>AND</b>
<b>Clinical criteria:</b>
Acalabrutinib must be initiated as a monotherapy for 1 Cycle with treatment in combination with obinutuzumab commencing at the start of <del>in</del> Cycle 2 Day 1
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a creatinine clearance 30 mL/min or greater,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage),
<b>OR</b>
Patient must have a creatinine clearance less than <del>CrCl</del> < 70 mL/min.
<b>Prescriber Instructions:</b> A patient may only qualify for PBS subsidised initiation treatment with this drug once in a lifetime under:
1. The untreated CLL/SLL initial or transitioning from non-PBS -subsidised supply restriction; or
2. The relapsed or refractory CLL/SLL initial treatment restriction.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ACALABRUTINIB					
<del>ACALABRUTINIB, Treatment of patients with previously untreated CLL or SLL, 100 mg capsule, oral administration 100 mg, capsule</del>	NEW	1	56	3	Calquence
		Max.qty (packs) multiplier = 2			
		Repeat increases: nil			
<b>Restriction Summary / Treatment of Concept:</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					

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<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative advice:</b> Special Pricing Arrangements apply.
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Condition:</b> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Indication:</b> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Treatment Phase:</b> First continuing treatment (treatment cycles 4 to 7 inclusive) in first-line therapy
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must cease upon disease progression
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be in combination with obinutuzumab for cycles 4 to 7. (refer to Product Information for timing of obinutuzumab and acalabrutinib doses),

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ACALABRUTINIB					
ACALABRUTINIB, Treatment of patients with previously untreated CLL or SLL, 100 mg capsule, oral administration 100 mg, capsule	NEW	1	56	5	Calquence
		Max.qty (packs) multiplier = 2 Repeat increases: nil			

**Restriction Summary / Treatment of Concept:**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative advice:</b> Special Pricing Arrangements apply.
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Condition:</b> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Indication:</b> <del>Patients with previously untreated CLL/SLL</del> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Treatment Phase:</b> <del>Grandfather</del> –Transitioning from non-PBS to PBS-subsidised supply in first-line therapy – Grandfather arrangements
<b>Clinical criteria:</b>
The treatment must be in combination with obinutuzumab or as monotherapy following 6 cycles of obinutuzumab (refer to Product Information for timing of acalabrutinib and obinutuzumab doses)
<b>AND</b>
<b>Clinical criteria:</b>
Patient must be considered unsuitable for fludarabine-based chemoimmunotherapy,

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<b>AND</b>
<b>Clinical criteria:</b>
The condition must have been untreated prior to initiating non-PBS-subsidised treatment with this drug for this condition.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have previously received non-PBS subsidised treatment with this drug for previously untreated CLL/SLL, or intolerance/adverse event requiring permanent discontinuation of venetoclax + obinutuzumab treatment prior to [PBS listing date of acalabrutinib]-Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [listing date].
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have had a creatinine clearance 30 mL/min or greater prior to initiating non-PBS-subsidised treatment with this drug for this condition,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have had a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage) prior to initiating non-PBS-subsidised treatment with this drug for this condition,
<b>OR</b>
Patient must have had a creatinine clearance less than CrCl < 70 mL/min prior to initiating non-PBS-subsidised treatment with this drug for this condition.
<b>Administrative advice:</b> Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the First or subsequent continuing treatment criteria
<b>Administrative advice:</b> This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria
<b>Prescriber Instructions:</b> A patient may only qualify for PBS subsidised initiation treatment once in a lifetime under: <ol style="list-style-type: none"> <li>1. The untreated CLL/SLL initial or transitioning from non-PBS-subsidised treatment restriction; or</li> <li>2. The relapsed or refractory CLL/SLL initial treatment restriction.</li> </ol>
<b>Restriction Summary / Treatment of Concept:</b>
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined Telephone/electronic via Online PBS Authorities
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative advice:</b> Special Pricing Arrangements apply.
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Condition:</b> Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Indication:</b> Patients with previously untreated CLL/SLL Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
<b>Treatment Phase:</b> Continuing Subsequent continuing treatment in first-line therapy
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition The treatment must cease upon disease progression
<b>AND</b>
<b>Clinical criteria:</b>

The treatment must be as monotherapy.

- 3.2 The resubmission proposed a special pricing arrangement. The proposed effective DPMQ of \$| is lower than the price proposed in the November 2021 resubmission (effective DPMQ: \$|), and the current relapsed/refractory CLL/SLL PBS listing (effective DPMQ: \$|).
- 3.3 The proposed restriction is narrower than the TGA indication, which does not restrict treatment on the basis of suitability for fludarabine-based chemoimmunotherapy, use in combination with obinutuzumab, CIRS score or renal function.
- 3.4 The proposed initial treatment restriction type (Authority Required) and clinical criteria are consistent with venetoclax. However, the proposed clinical criteria differ from the eligibility criteria for the ELEVATE-TN, which recruited patients aged ≥65 years (i.e., regardless of CIRS score or renal function) and patients aged <65 years with a CIRS score >6 or a creatinine clearance of 30 to 69 mL/min.
- 3.5 Additionally, the ELEVATE-TN trial required patients to have an ECOG score ≤2, while the proposed PBS restriction did not include a criterion regarding ECOG score.
- 3.6 There is a risk of acalabrutinib use outside of the proposed restriction as monotherapy. The evaluation considered that acalabrutinib monotherapy may be preferred in some patients due to lower toxicity compared with acalabrutinib + obinutuzumab, and given that it is an oral treatment that does not require hospital attendance for administration. Listing of acalabrutinib monotherapy was not requested in the current resubmission, but had been requested in the two previous submissions. The PBAC previously considered that acalabrutinib monotherapy was superior to chlorambucil + obinutuzumab in terms of progression-free survival (paragraph 7.8, acalabrutinib, Public Summary Document, November 2021 PBAC meeting), and that it was likely acalabrutinib monotherapy would be used in the majority of patients unsuitable for treatment with a purine analogue given the additional toxicity of acalabrutinib + obinutuzumab combination therapy together with the general frailty of the patient population (paragraph 7.3, acalabrutinib, Public Summary Document, July 2020 PBAC meeting). Updated results for acalabrutinib monotherapy in the ELEVATE-TN trial were presented as part of the resubmission, including the results of an updated MAIC comparing acalabrutinib monotherapy to venetoclax + obinutuzumab.
- 3.7 The Pre-Sub-Committee Response (PSCR) stated that while some patients may prefer acalabrutinib monotherapy, listing was only being sought for patients who are suitable for acalabrutinib + obinutuzumab because the combination provides superior progression-free survival and overall survival compared with acalabrutinib monotherapy, venetoclax + obinutuzumab, or chlorambucil + obinutuzumab. The PSCR further stated ‘acalabrutinib + obinutuzumab should be the regimen of choice unless there are tolerability concerns’. The ESC considered that the treatment of CLL/SLL is evolving, and clinicians may now be more likely to use obinutuzumab-containing regimens in older patients as there have been improvements in managing

the adverse events associated with obinutuzumab therapy. The ESC considered that some patients may cease the obinutuzumab component early (i.e., prior to completing six cycles) and noted that this occurred in the ELEVATE-TN trial, in which 4.5% of patients had less than 3 cycles of obinutuzumab and 10.1% had 3 to 5 cycles. However, the PBAC considered that it would be clinically appropriate to enable access to acalabrutinib monotherapy given it may be preferred by some patients due to lower toxicity versus the combination and given that it is an oral treatment.

- 3.8 The resubmission requested a grandfather restriction stating that an access program may be commenced if the PBAC recommends listing of acalabrutinib in this indication.

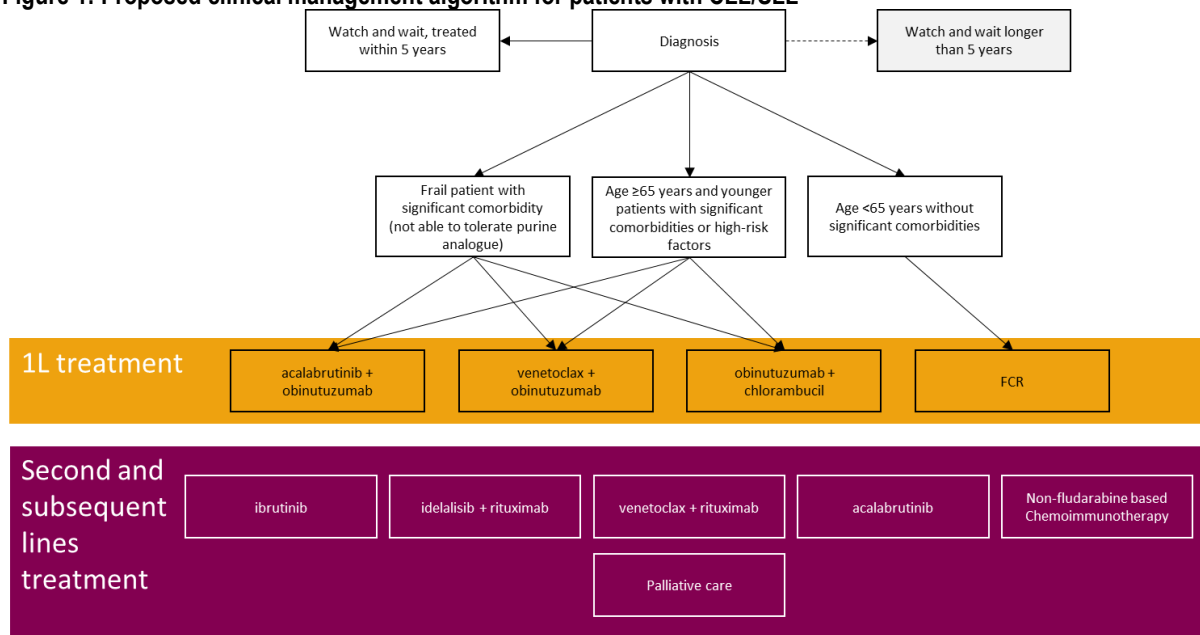
*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 CLL is characterised by the progressive accumulation of functionally incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, spleen, and liver. CLL and SLL are generally considered to be different manifestations of the same disease. In CLL, abnormal lymphocytes are predominantly found in blood, bone marrow and lymphoid tissue, whereas in SLL, abnormal lymphocytes are predominantly located in lymph nodes, bone marrow and other lymphoid tissue.
- 4.2 CLL is more common in men than women (63% versus 37%), with a mean age at diagnosis in Australia in 2018 of 71.0 years (males 70.2 years, females 72.4 years). The five-year relative survival rate in Australia for 2014 to 2018 was 85.4% (AIHW, 2022). Typical symptoms associated with CLL include fatigue, swollen lymph nodes, pain, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating, and unintentional weight loss. The resubmission noted that the results of a web-based survey of 1,482 CLL patients assessing the impact of CLL on the quality of life of patients suggest that CLL-related symptoms and comorbidities markedly reduce quality of life, with fatigue being the most recognised disease-related symptom (Shanafelt et al., 2007).
- 4.3 Characteristics associated with a worse prognosis include genetic factors (17p deletion/TP53 mutation, 11q deletion, unmutated IGHV), biochemical/cell surface markers (serum thymidine kinase, serum  $\beta$ 2 microglobulin), and patient characteristics (male sex, older age, worse ECOG performance score). Deletion of the short arm of chromosome 17 (17p deletion) is found in 5-8% of chemotherapy-naïve patients, and is associated with resistance to genotoxic chemotherapies, including conventional chemoimmunotherapy regimens (Hallek, 2015).
- 4.4 CLL/SLL is generally a slowly progressing cancer, with many patients managed with a 'watch and wait' approach until symptoms develop. The choice of therapy depends on a number of factors, including age, comorbidities, and the presence of prognostic genetic mutations.

- 4.5 The proposed PBS population comprises patients with previously untreated CLL/SLL who are unsuitable for treatment with fludarabine-based chemoimmunotherapy. The proposed population is broader than the proposed population in the November 2021 resubmission, which was limited to patients considered unsuitable for treatment with fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab; and patients who have permanently discontinued treatment with venetoclax + obinutuzumab due to intolerance.
- 4.6 Acalabrutinib is a small-molecule inhibitor of Bruton’s tyrosine kinase (BTK). In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. No other BTK inhibitors are PBS-listed for use in previously untreated patients with CLL/SLL. Obinutuzumab is a monoclonal antibody targeting the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre B and mature B lymphocytes.
- 4.7 The resubmission’s proposed clinical management algorithm is presented in Figure 1.

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



Source: Figure 1.4 of the resubmission.

1L = first line, CLL = chronic lymphocytic leukaemia, FCR = fludarabine + cyclophosphamide + rituximab, SLL = small lymphocytic leukaemia

- 4.8 The algorithm positioned acalabrutinib + obinutuzumab as an alternative to treatment with venetoclax + obinutuzumab and chlorambucil + obinutuzumab for patients who are unsuitable for treatment with fludarabine-based chemoimmunotherapy (i.e., frail patients with significant comorbidity who are unable to tolerate treatment with a purine analogue; patients aged ≥65 years; and patients aged <65 years with significant comorbidities or high-risk factors).
- 4.9 The ESC noted that, while listing was sought in the ‘unfit’ population, treatment guidelines (NCCN CLL guidelines 2022) recommend the use of acalabrutinib ±

obinutuzumab (or ibrutinib monotherapy, or venetoclax + obinutuzumab) as the preferred first-line therapies for all patients (regardless of age, presence of comorbidities, or presence of del17p/TP53 mutation). The ESC noted that none of these agents or combinations are currently PBS listed for first-line use in ‘fit’ patients. The ESC further noted that the key PBS-listed treatment in fit patients, FCR, is only included in the NCCN guidelines as a later-line option and is poorly tolerated and associated with a risk of cytopenia and secondary malignancies. The ESC considered that Australia lags international guidelines in providing access to small molecule inhibitors (BTK inhibitors and/or B-cell lymphoma 2 (BCL2) inhibitors) in the first-line treatment of patients with CLL and there is a high clinical need for alternate treatment options.

- 4.10 Further, the ESC noted that, in some cases, there may also be a gap in the PBS availability of small molecule inhibitors for patients who are young (<65 years) and unfit (CRS >6 and/or creatinine clearance <70 mL/min) despite this being a group with a high potential to benefit in the context of an indolent condition. The proposed restriction requires patients to be ‘unsuitable for fludarabine-based chemoimmunotherapy’, which may in clinical practice include consideration of patient age (though age is not specifically referred to in the proposed PBS restriction). Further, these patients may not be able to access BTK inhibitors (acalabrutinib or ibrutinib) or venetoclax in the relapsed/refractory setting (e.g., depending on response/progression-free interval following first-line therapy, del17p status or presence of specific autoimmune conditions). The ESC considered that, while the listing requested in the resubmission aligned to a degree with the clinical evidence provided, broader access to regimens containing small molecule inhibitors across both fit and unfit patients in the first-line setting may help address clinical need and equity of access.
- 4.11 The ESC noted that a submission for ibrutinib is also on the agenda for the November 2022 PBAC meeting, which is requested for use in combination with venetoclax, for the treatment of previously untreated CLL/SLL.

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

## **5 Comparator**

- 5.1 The resubmission nominated venetoclax + obinutuzumab as the main comparator. The main arguments provided in support of this nomination were:
- Venetoclax + obinutuzumab is the treatment most likely to be replaced by acalabrutinib + obinutuzumab, based on a higher market share compared to chlorambucil + obinutuzumab (66.2% versus 33.8%, based on obinutuzumab 2021 PBS dispensing data).
  - The PBAC previously considered that venetoclax + obinutuzumab was superior to chlorambucil + obinutuzumab in terms of progression-free survival.

- 5.2 Venetoclax + obinutuzumab is an appropriate main comparator. Venetoclax + obinutuzumab was included as a near-market comparator in the July 2020 acalabrutinib submission. While venetoclax + obinutuzumab was not nominated as a comparator in the November 2021 resubmission (on the basis that the requested PBS restriction required patients to be unsuitable for treatment with venetoclax + obinutuzumab), the PBAC had considered that, based on the proposed restriction, venetoclax + obinutuzumab was also a relevant comparator.
- 5.3 The evaluation noted that ibrutinib monotherapy is a potential near-market comparator for patients with 17p deletion. Ibrutinib received a positive recommendation at the November 2019 PBAC meeting for the treatment of previously untreated patients with 17p deletion, but is not currently listed on the PBS. At the November 2021 meeting, the PBAC extended the positive recommendation for an additional 12 months (PBAC Outcomes, November 2021 PBAC meeting). The July 2020 acalabrutinib submission used a cost-minimisation approach to compare acalabrutinib and ibrutinib in patients with 17p deletion.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented evidence supporting the use of BTK inhibitors as a class for the first-line treatment of CLL/SLL and discussed first-line therapies that are recommended in global guidelines. In particular, the clinician discussed that access to a BTKi in the first-line setting is a major area of unmet need. In response to the Committee's questions, the clinician outlined that access to BTKi monotherapy is important; while combination therapy with a BTKi + obinutuzumab may be the optimal choice for some patients, for others monotherapy may be preferred based on their preferences. Further, the clinician outlined that the CIRS score, which is included in the existing restriction for venetoclax + obinutuzumab, was developed to assess the ability of a patient to tolerate chemoimmunotherapy and is less relevant for targeted agents. The PBAC considered that the hearing was informative as it provided a current clinical perspective on the role of BTK inhibitors as a class in the midst of a changing clinical landscape.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (15) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with acalabrutinib including improved quality of life and a generally manageable adverse event profile. The comments outlined the advantages compared with FCR including improved clinical outcomes (particularly in patients with specific mutations) and fewer adverse events. The comments also outlined that acalabrutinib (without obinutuzumab) is easy to administer (tablet

formulation) with less intensive monitoring requirements than other CLL treatments, which is a particular advantage for patients in rural and remote areas.

- 6.3 The PBAC noted the advice received from Lymphoma Australia and the Leukaemia Foundation that many patients with CLL/SLL are unsuitable for FCR, some patients have specific mutations (e.g., del17p) that do not respond to FCR, and that FCR is associated with significant risk of adverse events. The comments outlined that there is currently a gap in PBS access to therapies that are recommended as best clinical practice. The comments noted that acalabrutinib is effective and generally tolerable.
- 6.4 The PBAC recalled that a clinician consultation was held on 1 December 2022 to discuss the treatment of CLL /SLL in relation to the existing PBS treatment algorithm and the new drug regimens proposed for PBS-listing in the context of the evolving treatment landscape. The key points were:
- The clinicians emphasised that FCR is no longer a preferred regimen in any patient group, which creates a significant access issue for young and/or fit patients who do not meet the existing PBS criteria for Bruton’s tyrosine kinase inhibitors (BTKi) or venetoclax (BCL-2i). The clinicians noted that, while the clinical need is highest in patients with poor risk cytogenetics, it would not be appropriate to limit access to BTKi and /or venetoclax therapy to these specific groups given the high clinical need across the broader young, fit population.
  - The clinicians indicated that the existing PBS criteria around ‘inappropriate for fludarabine-based chemoimmunotherapy’ and ‘unsuitable for treatment with a purine analogue’ are no longer relevant to current clinical practice.
  - The clinicians advised that there is a lack of clinical trial data available to differentiate between regimens or determine which particular regimen would be preferable in a particular patient group/setting. Overall, the clinicians considered that it would be preferable to have a range of options available for all patients with CLL/SLL. The clinicians noted that any treatment option containing a BTKi and/or venetoclax would be preferable to FCR.
  - The clinicians outlined that it would be appropriate to re-treat patients with venetoclax or BTKi therapy if they had progressed following these therapies (unless discontinued due to poor tolerability). The clinicians indicated that a longer duration of initial response was an indicator for a higher probability of responding to that same therapy again (and vice versa). The clinicians indicated that there were no firm data regarding a time-frame for a recurrence-free period after which it would be appropriate to re-treat with the same agent and advised that a range of variables would be taken into account such as patient age and treatment intent.

### ***Clinical trials***

- 6.5 The resubmission was based on the following comparisons of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab:

- An unanchored, unadjusted (naïve) indirect comparison and an unanchored MAIC of acalabrutinib + obinutuzumab (ELEVATE-TN) versus venetoclax + obinutuzumab (CLL-14), at a median duration of follow-up of 28.3 months and 28.1 months, respectively. These comparisons were previously considered at the July 2020 PBAC meeting.
  - An unanchored, unadjusted (naïve) indirect comparison and an unanchored MAIC of acalabrutinib + obinutuzumab (ELEVATE-TN) versus venetoclax + obinutuzumab (CLL-14), at a median duration of follow-up of 46.9 months and 39.6 months, respectively. Results from this data cut of the ELEVATE-TN trial were considered at the November 2021 PBAC meeting, however no comparison was made to venetoclax + obinutuzumab in that submission.
  - An unanchored, unadjusted (naïve) indirect comparison of acalabrutinib + obinutuzumab (ELEVATE-TN) versus venetoclax + obinutuzumab (CLL-14) at a median duration of follow-up of 58.2 months and 52.4 months, respectively.
- 6.6 During the evaluation, an additional publication for the CLL-14 trial was identified (Al-Sawaf et al., 2022) which reported outcomes at a median follow-up of 65.4 months, the results of which are also presented below.
- 6.7 Naïve comparisons and unanchored MAICs were also presented for acalabrutinib monotherapy versus venetoclax + obinutuzumab.
- 6.8 Details of the trial reports presented in the resubmission are provided 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.
	Xu W. ELEVATE-TN high level results (11 September 2020 data cut).	PowerPoint slides, Attachment 2D of the resubmission, 7 January 2021.
	Sharman JP, Egyed M, Jurczak W, Skarbnik A et al. Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: 5-year follow-up of ELEVATE-TN.	Journal of Clinical Oncology 2022; 40(16_suppl).
	Sharman J, Egyed M, Jurczak W, Sharbnik A et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukaemia: ELEVATE-TN four-year follow up.	Journal of Clinical Oncology 2021; 39 (15_suppl): 7509-7509.
	Sharman J, Egyed M, Jurczak W, Sharbnik A et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial.	The Lancet 2020; 395 (10232): 1278-1291.
CLL-14	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.
	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):1188-200.
	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.
	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.
	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.

Source: Table 2.5 of the resubmission.

Selected references to conference abstracts omitted.

6.9 The key features of the ELEVATE-TN and CLL-14 trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Acalabrutinib + obinutuzumab vs acalabrutinib monotherapy vs chlorambucil + obinutuzumab</b>						
ELEVATE-TN	535	Phase 3, randomised, open-label trial. Median duration of follow-up: - 28.3 months (February 2019 data cut) - 46.9 months (September 2020 data cut) - 58.2 months (October 2021 data cut)	Unclear	- Age ≥ 65 years, or 18-65 years meeting additional criteria (CrCl of 30-69 mL/min or CIRS score >6). - Active CD20+ CLL disease requiring treatment. - ECOG score ≤2. - No prior systemic treatment for CLL.	- Progression-free survival - Overall response rate - Overall survival - Time to next treatment - Adverse events - Health-related quality of life (FACIT-Fatigue, EORTC QLQ-C30, EQ-5D-3L)	- Progression-free survival - Overall survival - Time to next treatment - Time to treatment discontinuation
<b>Venetoclax + obinutuzumab versus chlorambucil + obinutuzumab</b>						
CLL-14	432	Phase 3, randomised, open-label trial. Median duration of follow-up: - 28.1 months (Fischer et al., 2019) - 39.6 months (Al-Sawaf et al., 2020) - 52.4 months (Al-Sawaf et al., 2021) - 65.4 months (Al-Sawaf et al., 2022)	Unclear	- Age ≥ 18 years. - CIRS score >6 or CrCl <70 mL/min. - CLL disease requiring treatment. - Documented previously untreated CLL.	- Progression-free survival - Overall response rate - Overall survival - Time to next treatment - MRD response rate - Duration of response - Event-free survival - Adverse events - HRQOL (MDASI, EORTC QLQ-C30, EQ-5D-5L).	- Progression-free survival - Overall survival - Time to next treatment

Source: Table S1 of the ELEVATE-TN interim clinical study report.

CD = cluster of differentiation, CIRS = cumulative illness rating scale, CLL = chronic lymphocytic leukaemia, CrCl = creatinine clearance, ECOG = European Cooperative Oncology Group, EQ-5D-3L = EuroQol five-dimension 3-level, EORTC = European Organisation for Research and Treatment of Cancer, FACIT = Functional Assessment of Chronic Illness Therapy, MDASI = MD Anderson Symptom Inventory = QLQ-C30 = quality of life questionnaire Core 30

- 6.10 The ELEVATE-TN and CLL-14 trials had an unclear risk of bias. As the trials were open label, investigators, patients, and study personnel were not blinded to treatment allocation, which may have influenced the treatment of patients in the trial. Assessments made by study investigators (who were not blinded to treatment allocation) were at high risk of bias. Each trial included blinded assessments by an independent review committee, which had a lower risk of assessment bias. However, longer term progression-free survival results were based on investigator assessments.
- 6.11 There were differences in the eligibility criteria between the ELEVATE-TN and CLL-14 trials. While the ELEVATE-TN and CLL-14 trials both recruited adult patients with previously untreated CLL, the ELEVATE-TN trial included patients who were aged ≥65 years, and patients aged <65 years if they met additional criteria (creatinine clearance of 30 to 69 mL/min or a CIRS score >6). Patients recruited for the CLL-14 trial were required to have a CIRS score >6 or a creatinine clearance <70 mL/min.
- 6.12 The median age of patients in the ELEVATE-TN trial was 70 years and 61% of the trial population was male. The disease was Rai Stage 3 or 4 in 47% of patients, 32% had

bulky disease ( $\geq 5$ cm), 94% had an ECOG score of 0 to 1, 9% had 17p deletion, 63% had unmutated IGHV, and 75% had  $\beta 2$ -microglobulin  $> 3.5$  mg. The median age of patients in the CLL-14 trial was 72 years and 67% of the trial population was male. The disease was Binet Stage A in 21% of patients (Stage B: 36%; Stage C 43%), 88% had an ECOG score of 0 to 1, 8% had 17p deletion, 60% had unmutated IGHV, and 60% had  $\beta 2$ -microglobulin  $> 3.5$  mg. Data for a number of characteristics, including bulky disease, Rai Stage, mean age, race and geographic region were not available in publications for the CLL-14 trial.

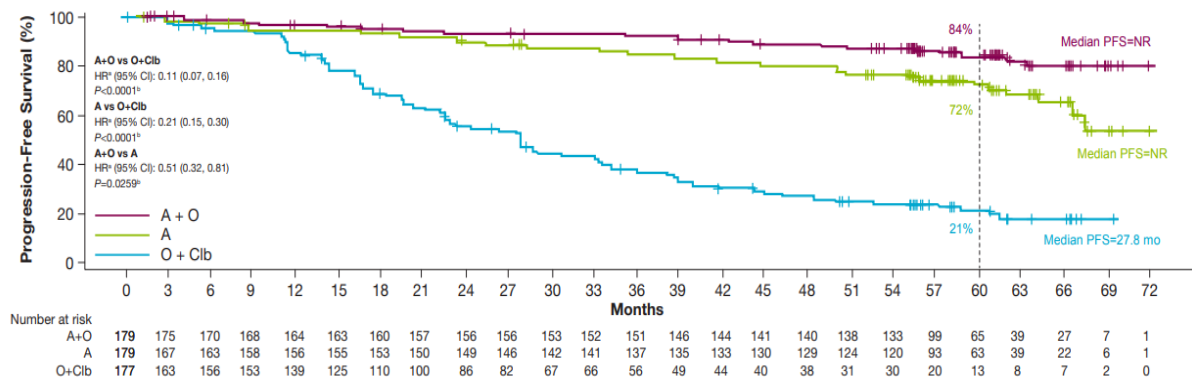
- 6.13 While the proportion of patients in the ELEVATE-TN trial with a CIRS score  $> 6$  was not reported for the full trial population, data provided for the MAIC analysis indicates that the proportion of patients with a CIRS score  $> 6$  in the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms was substantially lower than the proportion in the venetoclax + obinutuzumab arm of the CLL-14 trial (47% versus 86%).
- 6.14 There were differences between the trials in the duration of treatments. In the CLL-14 trial, treatment with venetoclax was based on a fixed treatment duration of 12 cycles (48 weeks), whereas treatment with acalabrutinib in the ELEVATE-TN trial was ongoing until disease progression or unacceptable toxicity. At a median follow-up of 58.2 months, treatment was ongoing in 64.8% of patients treated with acalabrutinib + obinutuzumab and 59.8% of patients treated with acalabrutinib monotherapy. Patients in the chlorambucil + obinutuzumab arm of the ELEVATE-TN trial received up to 6 cycles (24 weeks) of chlorambucil, whereas patients in the chlorambucil + obinutuzumab arm of the CLL-14 trial received up to 12 cycles (48 weeks) of chlorambucil.
- 6.15 Patients in the chlorambucil + obinutuzumab arm of the ELEVATE-TN trial who had independent review committee-assessed disease progression were eligible to receive crossover treatment with acalabrutinib monotherapy (100 mg twice daily) until disease progression or unacceptable toxicity. At the October 2021 data cut, 41% of patients in the chlorambucil + obinutuzumab treatment arm had crossed over to receive acalabrutinib treatment. Crossover was not permitted in the CLL-14 trial.
- 6.16 As in the November 2021 resubmission, the resubmission argued that it is difficult to define a minimal clinically important difference (MCID) for efficacy outcomes (i.e., progression-free survival, overall survival, overall response rate, time to next treatment), as there is no generally accepted level of clinically important difference for efficacy outcome measures for CLL patients. As in the November 2021 resubmission, the current resubmission proposed an MCID of approximately 18 months for progression-free survival, based on the sample size calculation for the ELEVATE-TN trial, which was calculated according to a target hazard ratio of 0.6 for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab (equating to an approximately 18-month absolute increase in median progression-free survival).

### Comparative effectiveness

#### Naïve comparison of PFS and OS from ELEVATE-TN and CLL-14 (median follow-up: 58.2 and 65.4 months, respectively)

6.17 Kaplan-Meier plots of investigator-assessed progression-free survival for the ELEVATE-TN trial and the CLL-14 trial are presented in Figure 2 and Figure 3, respectively.

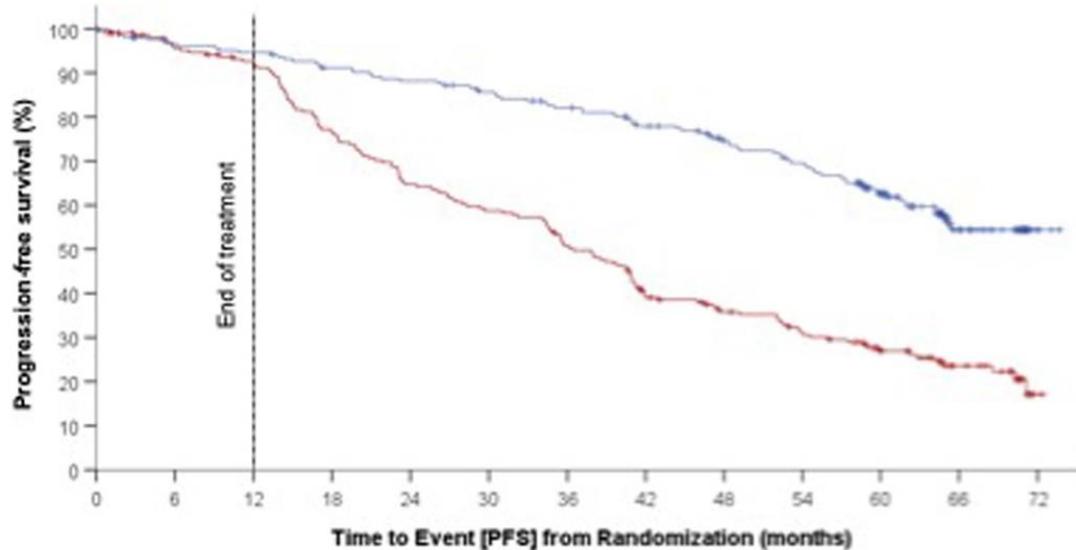
Figure 2: Kaplan-Meier plot of investigator-assessed progression-free survival for the ELEVATE-TN trial at median follow-up of 58.2 months



Source: Figure 2.4, p72 of the resubmission.

A = acalabrutinib, CI = confidence interval, Clb = chlorambucil, HR = hazard ratio, NR = not reported, O = obinutuzumab, PFS = progression-free survival

Figure 3: Kaplan-Meier plot of investigator-assessed progression-free survival for the CLL-14 trial at a median follow-up of 65.4 months



Patients at risk	
Ven-Obi	216 196 192 183 177 169 160 147 134 123 97 35 4
Clb-Obi	216 195 185 154 130 118 101 75 64 53 39 21 1

Source: Al-Sawaf et al. (2022).

Clb = chlorambucil, Obi = obinutuzumab, Ven = venetoclax

6.18 The results for investigator-assessed progression-free survival for the ELEVATE-TN and CLL-14 trials are summarised in Table 5.

**Table 5: Investigator-assessed progression-free survival results for the ELEVATE-TN and CLL-14 trials**

	ELEVATE-TN			CLL-14	
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)	VEN + OBI (N=216)	CHL + OBI (N=216)
Median duration of follow-up, months (range)	58.2 (NR)			65.4 (NR)	
Events, n (%)	NR	NR	NR	52 (NR)	132 (NR)
Median PFS, months (95% CI)	Not reached	Not reached	27.8 (22.6, 28.8)	Not reached	36.4 (NR)
HR vs CHL + OBI (95% CI)	<b>0.11 (0.07, 0.16)</b>	<b>0.21 (0.15, 0.30)</b>	-	<b>0.35 (0.26,0.46)</b>	-
KM estimate of PFS					
- 12 months, % (95% CI)	95.4 (91.1, 99.5)	94.7 (90.1, 97.2)	85.5 (79.1, 90.0)	NR	NR
- 24 months, % (95% CI)	91.9 (86.7, 95.1)	90.4 (84.9, 94.0)	54.7 (46.7, 62.0)	NR	NR
- 36 months, % (95% CI)	90.9 (85.3, 94.5)	87.6 (81.0, 92.1)	36.9 (26.6, 47.1)	NR	NR
- 48 months, % (95% CI)	87 (NR)	78 (NR)	25 (NR)	NR	NR
- 60 months, % (95% CI)	84 (NR)	72 (NR)	21 (NR)	62.6 (NR)	27.0 (NR)

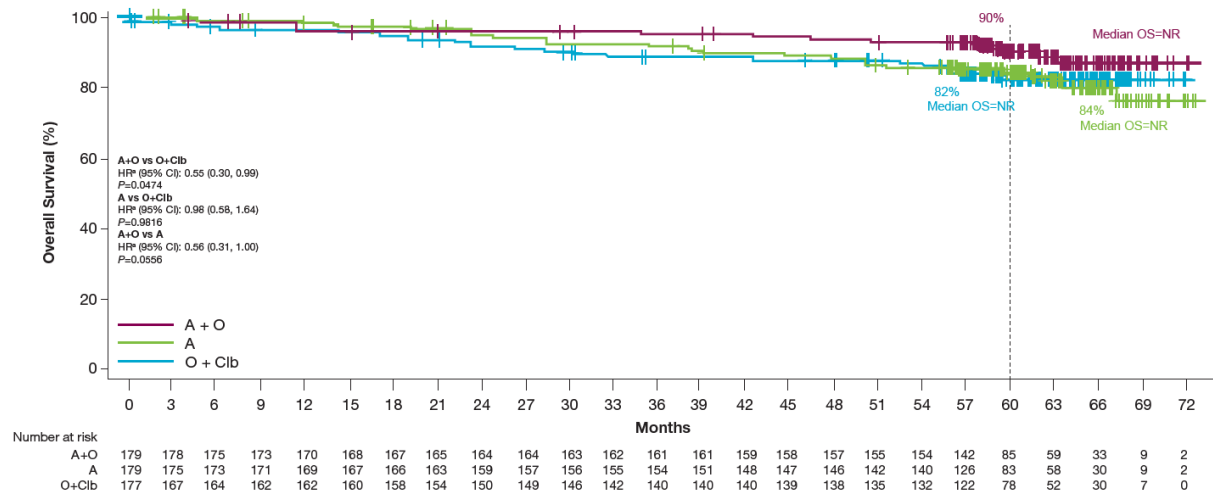
Source: Table 2.23, Table 2.24 of the resubmission; Al-Sawaf et al. (2022).

ACAL = acalabrutinib, CHL = chlorambucil, CI = confidence interval, HR = hazard ratio, KM = Kaplan-Meier, NE = not estimable, NR = not reported, OBI = obinutuzumab, PFS = progression-free survival

Bold indicates statistically significant results.

- 6.19 At a median duration of follow-up of 58.2 months in the ELEVATE-TN trial, investigator-assessed progression-free survival was statistically significantly longer among patients in the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms compared to the chlorambucil + obinutuzumab arm. A post hoc analysis based on the October 2021 data cut (Sharman et al., 2022) was suggestive of a statistically significant difference in favour of acalabrutinib + obinutuzumab compared to acalabrutinib monotherapy (HR = 0.51 [95% CI: 0.32, 0.81]).
- 6.20 At a median duration of follow-up of 65.4 months in the CLL-14 trial, investigator-assessed progression-free survival was statistically significantly longer among patients in the venetoclax + obinutuzumab arm compared to the chlorambucil + obinutuzumab arm.
- 6.21 Based on a naïve comparison of 60-month Kaplan-Meier estimates for the ELEVATE-TN and CLL-14 trials, progression-free survival was numerically higher for acalabrutinib + obinutuzumab compared to venetoclax + obinutuzumab (84% versus 62.6%). However, this comparison should be interpreted with caution due to differences in trial inclusion criteria and patient characteristics between the trials.
- 6.22 Kaplan-Meier plots of overall survival for the ELEVATE-TN trial and the CLL-14 trial are presented in Figure 4 and Figure 5, respectively.

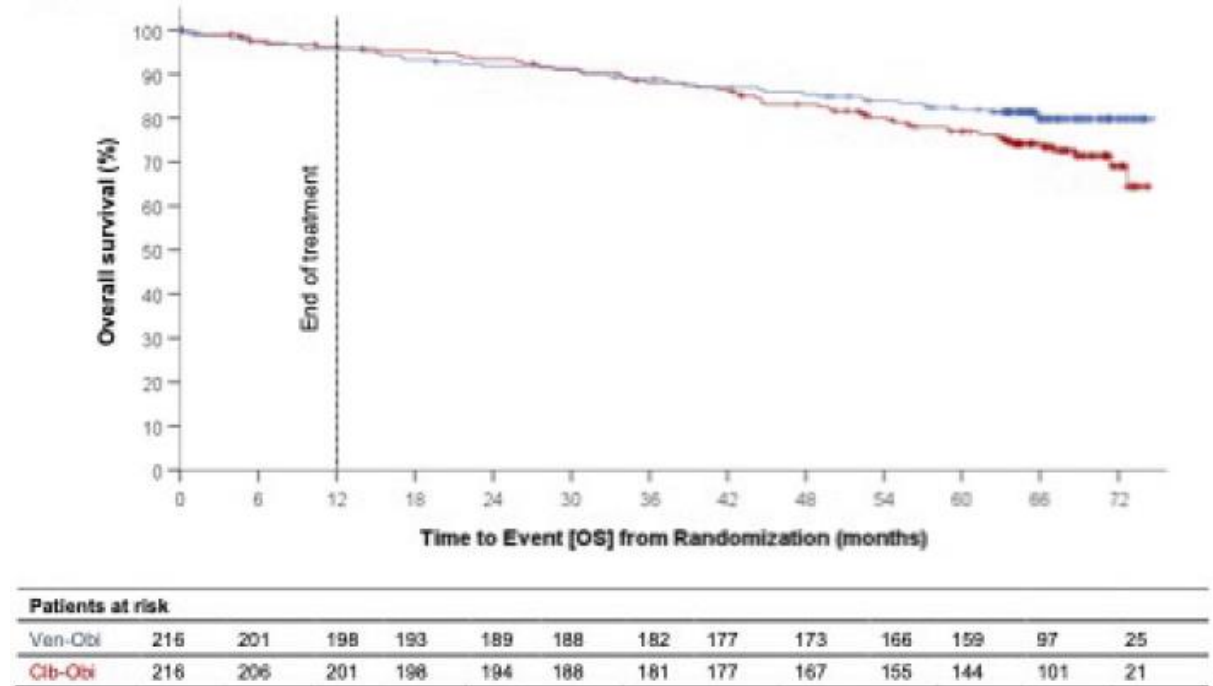
Figure 4: Kaplan-Meier plot of overall survival for the ELEVATE-TN trial at median follow-up of 58.2 months



Source: Figure 2.4 of the resubmission.

A = acalabrutinib, CI = confidence interval, Clb = chlorambucil, HR = hazard ratio, NR = not reported, O = obinutuzumab, OS = overall survival

Figure 5: Kaplan-Meier plot of overall survival for the CLL-14 trial at a median follow-up of 65.4 months



Source: Al-Sawaf et al. (2022).

Clb = chlorambucil, Obi= obinutuzumab, PFS = progression-free survival, Ven = venetoclax

6.23 The results for overall survival for the ELEVATE-TN and CLL-14 trials are summarised in Table 6.

**Table 6: Overall survival results for the ELEVATE-TN and CLL-14 trials**

Cohort	ELEVATE-TN			CLL-14	
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)	VEN + OBI (N=216)	CHL + OBI (N=216)
Median duration of follow-up, months (range)	58.2 (NR)			65.4 (NR)	
Death, n (%)	NR	NR	NR	40 (NR)	57 (NR)
Median OS, months (95% CI)	Not reached	Not reached	Not reached	Not reached	Not reached
HR vs CHL + OBI (95% CI)	0.55 (0.30, 0.99)	0.98 (0.58, 1.64)	-	0.72 (0.48, 1.09)	-
KM estimate of OS					
- 12 months, % (95% CI)	96.1 (91.9, 98.1)	98.3 (94.8, 99.4)	96.5 (92.4, 98.4)	NR	NR
- 24 months, % (95% CI)	94.9 (90.5, 97.3)	94.7 (90.2, 97.2)	91.7 (86.3, 95.0)	NR	NR
- 36 months, % (95% CI)	94.3 (89.7, 96.9)	93.5 (88.6, 96.3)	88.1 (80.7, 92.8)	NR	NR
- 48 months, % (95% CI)	93 (NR)	88 (NR)	88 (NR)	NR	NR
- 60 months, % (95% CI)	90 (NR)	84 (NR)	82 (NR)	81.9 (NR)	77.0 (NR)

Source: Table 2.30, Table 2.31 of the resubmission; Al-Sawaf et al. (2022).

ACAL = acalabrutinib, CHL = chlorambucil, CI = confidence interval, HR = hazard ratio, KM = Kaplan-Meier, NE = not estimable, NR = not reported, OBI = obinutuzumab, OS = overall survival

- 6.24 At a median duration of follow-up of 58.2 months in the ELEVATE-TN trial, there was a statistically significant difference in overall survival for acalabrutinib + obinutuzumab compared to chlorambucil + obinutuzumab, but not for acalabrutinib monotherapy compared to chlorambucil + obinutuzumab. A post hoc analysis comparing acalabrutinib + obinutuzumab versus acalabrutinib (Sharman et al., 2022) favoured acalabrutinib + obinutuzumab, but the difference was not statistically significant (HR = 0.56 [95% CI: 0.31, 1.00]). Overall survival results are likely to have been affected by differences in post-progression treatments received by patients who had experienced disease progression, including crossover of patients in the chlorambucil + obinutuzumab arm to receive acalabrutinib. As such, the ESC considered that the overall survival results were difficult to interpret.
- 6.25 At a median duration of follow-up of 65.4 months in the CLL-14 trial, there was no statistically significant difference in overall survival for venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab.
- 6.26 Based on a naïve comparison of 60-month Kaplan-Meier estimates for the ELEVATE-TN and CLL-14 trials, overall survival was numerically higher for acalabrutinib + obinutuzumab compared to venetoclax + obinutuzumab (90% versus 81.9%). However, the results of the naïve comparison should be interpreted with caution due to differences in trial inclusion criteria, patient characteristics, and subsequent anti-leukaemic treatments between the trials.

### Other outcomes from ELEVATE-TN and CLL-14 (various data cuts)

- 6.27 Investigator-assessed overall response rates for the ELEVATE-TN trial at the February 2019 data cut (median follow-up of 28.3 months) and the CLL-14 trial at a median follow-up of 28.1 months are presented in Table 7. Overall response rate data for the CLL-14 trial was only available at a median follow-up of 28.1 months.

**Table 7: Investigator-assessed overall response rate results for the ELEVATE-TN trial (median follow-up 28.3 months) and CLL-14 trials (median follow-up 28.1 months)**

	ELEVATE-TN			CLL-14 <sup>a</sup>	
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)	VEN + OBI (N=216)	CHL + OBI (N=216)
Median duration of follow-up, months (range)	28.5 (1.7-40.3)	28.4 (0.1-40.8)	28.0 (0.0-40.4)	28.1 (0.0-35.9)	
CR or CRi rate, n (%)	43 (24.0)	14 (7.8)	23 (13.0)		
Overall response rate, n (%)	172 (96.1)	160 (89.4)	146 (82.5)	183 (84.7)	154 (71.3)
Difference vs comparator arm (95% CI)	<b>13.6</b> <b>(7.3, 19.9)</b>	6.9 (-0.3, 14.1)	-	<b>13.4</b> <b>(5.5, 21.4)</b>	-

Source: Table 2.34, Table 2.35, Table 2.36 of the resubmission.

ACAL = acalabrutinib, CHL = chlorambucil, CI = confidence interval, CR = complete response; CRi = CR with incomplete blood count recovery; NR = not reported, OBI = obinutuzumab

<sup>a</sup> Overall response assessed 3 months after treatment completion.

- 6.28 At a median follow-up of 28.3 months in the ELEVATE-TN trial, a higher proportion of patients in the acalabrutinib + obinutuzumab arm achieved an overall response (96.1%) compared to the acalabrutinib (89.4%) and chlorambucil + obinutuzumab arms (82.5%). At a median follow-up of 28.1 months in the CLL-14 trial, a higher proportion of patients in the venetoclax + obinutuzumab arm achieved an overall response (84.7%) compared to the chlorambucil + obinutuzumab arm (71.3%).
- 6.29 Acalabrutinib + obinutuzumab was associated with higher rates of complete response (CR) and CR without incomplete bone marrow recovery (CRi) than acalabrutinib monotherapy (24% versus 7.8%, respectively) at a median follow-up of 28.3 months. In those patients with CR or CRi, acalabrutinib + obinutuzumab was associated with a higher proportion of patients being minimal residual disease (MRD) negative than acalabrutinib monotherapy (56% versus 7%, respectively).<sup>1</sup>
- 6.30 Based on investigator-assessed outcomes at a median follow-up of 52.8 months in the ELEVATE-TN trial, the overall response rate was higher in the acalabrutinib + obinutuzumab (96.1%) and acalabrutinib monotherapy arms (89.9%), compared to the chlorambucil + obinutuzumab arm (83.1%). The difference was statistically significant for the comparison of acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab (p<0.001) and marginally statistically significant for acalabrutinib monotherapy versus chlorambucil + obinutuzumab (p=0.0499).
- 6.31 Time to next anti-leukaemic treatment for the ELEVATE-TN trial at the September 2020 data cut (median follow-up 46.9 months) and the CLL-14 trial based on a median follow-up of 65.4 months are presented in Table 8. Time to next treatment results for

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<sup>1</sup> Sharman JP, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020 Apr 18;395(10232):1278-1291. doi: 10.1016/S0140-6736(20)30262-2. Accessed at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8151619/#SD1F>

the October 2021 data cut of the ELEVATE-TN trial were not provided in the resubmission.

**Table 8: Time to next treatment results for the ELEVATE-TN trial (median follow-up of 46.9 months) and the CLL-14 trial (median follow-up 65.4 months)**

Cohort	ELEVATE-TN			CLL-14	
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)	VEN + OBI (N=216)	CHL + OBI (N=216)
Median duration of follow-up, months (range)	46.9 (NR)			65.4 (NR)	
Total events, n (%)	19 (10.6)	39 (21.8)	101 (57.1)	NR	NR
Median TTNT, months (95% CI)	Not reached	Not reached	35.8 (29.7, 44.1)	NR	NR
Stratified HR vs CHL + OBI (95% CI)	NR	NR	-	0.42 (0.31, 0.57)	-
KM estimate of TTNT					
- 12 months, % (95% CI)	94.9 (90.5, 97.3)	94.3 (89.7, 96.9)	92.9 (87.9, 95.9)	NR	NR
- 24 months, % (95% CI)	93.2 (88.4, 96.1)	90.2 (84.7, 93.8)	67.0 (59.2, 73.6)	NR	NR
- 36 months, % (95% CI)	90.0 (80.0, 95.2)	86.3 (79.2, 91.1)	50.2 (40.3, 59.3)	NR	NR
- 48 months, % (95% CI)	-	-	-	NR	NR
- 60 months, % (95% CI)	-	-	-	72.1 (NR)	42.8 (NR)

Source: Table 2.40 of the resubmission.

ACAL = acalabrutinib, CHL = chlorambucil, CI = confidence interval, HR = hazard ratio, KM = Kaplan-Meier, NE = not estimable, OBI = obinutuzumab, TTNT = time to next treatment

- 6.32 At 36 months in the ELEVATE-TN trial, a higher proportion of patients in the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms (90.0% and 86.3%, respectively) had not initiated subsequent anti-cancer treatment, compared to 50.2% in the chlorambucil + obinutuzumab arm.
- 6.33 At 60 months in the CLL-14 trial, a higher proportion of patients in the venetoclax + obinutuzumab arm had not initiated subsequent anti-cancer treatment compared to patients in the chlorambucil + obinutuzumab arm (72% versus 43%). The results of a post hoc indirect comparison presented in the resubmission was suggestive of a statistically significant difference in time to next treatment favouring acalabrutinib + obinutuzumab (HR = 0.35 [95% CI: 0.28, 0.44]).
- 6.34 No new data for health-related quality of life outcomes were presented for the ELEVATE-TN trial in the resubmission. Patients across all three arms showed improvements in the FACIT-Fatigue Global Fatigue Score that exceeded the nominated clinically important difference of 3 points. There were no statistically significant differences between groups for any of the FACIT-Fatigue domains. For the EORTC QLQ-C30, statistically significant differences favouring chlorambucil + obinutuzumab were noted for role functioning at Week 96, fatigue at Week 24 and diarrhoea at Week 24 compared to acalabrutinib + obinutuzumab, and for role functioning at Week 96 and diarrhoea at Week 24 compared to acalabrutinib monotherapy. There were no statistically significant differences between groups for the EQ-5D visual analogue scale scores at Week 24 or Week 96. Results for the change from baseline in EQ-5D-5L overall scores were not provided.

- 6.35 Quality of life outcomes in the CLL-14 trial were assessed using the EORTC QLQ-C30 and the MD Anderson Symptom Inventory (MDASI). At the start of treatment, EORTC QLQ-C30 scale scores for physical functioning, role functioning and global health status/quality of life (GHS/QoL) were comparable between treatment arms. Baseline levels of physical and role functioning were maintained throughout treatment and follow-up, with no relevant improvement or deterioration. On average, patients treated with venetoclax + obinutuzumab had an improvement of at least eight points in GHS/QoL at cycle three, compared to cycle eight for the chlorambucil + obinutuzumab arm. Based on MDASI scores, CLL symptoms, core cancer symptoms, and symptom interference were generally low and comparable between treatment arms at baseline and were maintained throughout treatment and follow-up.

### **Matching-adjusted indirect comparisons**

- 6.36 MAICs for acalabrutinib +/- obinutuzumab versus venetoclax + obinutuzumab based on a median follow-up of 28.3 months for the ELEVATE-TN trial and 28.1 months for the CLL-14 trial were previously considered by the PBAC as part of the July 2020 PBAC submission. The current resubmission re-presented the results of the 28-month MAICs, along with updated MAIC results based on the September 2020 data cut for the ELEVATE-TN trial (median follow-up of 46.9 months) and outcomes for the CLL-14 trial based on a median follow-up of 39.6 months. It is unclear why the MAIC analyses were not conducted using the more recent data for the ELEVATE-TN and CLL-14 trials (i.e., the October 2021 data cut for ELEVATE-TN and the results reported by Al-Sawaf et al., 2021).
- 6.37 In July 2020, the PBAC had considered that the MAICs of both acalabrutinib monotherapy and acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab were highly uncertain. At that time, the PBAC had noted the heterogeneity between the ELEVATE-TN and CLL-14 trials which resulted in poor overlap between the trial populations and small effective sample sizes for the MAICs, and considered that it was unclear whether all relevant prognostic and effect modifier variables had been identified. In addition, the PBAC noted that although there were no statistically significant differences, no non-inferiority margins had been proposed and the confidence intervals were wide. Overall, the PBAC had considered that the efficacy and safety clinical claims based on the MAICs could not be supported (paragraph 7.9, acalabrutinib, Public Summary Document, July 2020 PBAC meeting).
- 6.38 The updated MAICs excluded 7 patients in the acalabrutinib + obinutuzumab arm and 3 patients in the acalabrutinib monotherapy arm due to missing baseline characteristic data. The MAICs presented in the July 2020 submission excluded 96 patients in the acalabrutinib + obinutuzumab arm and 83 patients in the acalabrutinib monotherapy arm due to missing patient data and differences in eligibility criteria between the ELEVATE-TN and CLL-14 trials. The resubmission did not adequately address the reasons for the difference in the number of excluded patients between the updated MAICs and the MAICs included in the July 2020 submission.

- 6.39 The resubmission stated that in order to conserve the effective sample size, the updated MAIC matched on fewer variables compared with the original MAIC. The resubmission noted that variables including age, sex, 17p deletion status, complex karyotype status and CIRS score were not matched in the updated MAIC analysis, but argued that these variables are unlikely to be treatment effect modifiers, and as such, matching for these variables is not expected to significantly change the conclusion of the MAICs. The evaluation and the ESC considered this was not reasonable. Unanchored MAICs should adjust for all effect modifiers and prognostic variables in order to reliably predict outcomes. Failure to adjust for all prognostic and effect modifier variables leads to an unknown amount of bias in the unanchored estimate. The resubmission did not adequately justify the decision to exclude relevant prognostic variables such as age, sex, disease stage, 17p deletion status and CIRS score from matching. The evaluation and the ESC considered that the failure to match for important prognostic variables suggests that the results of the MAICs are unlikely to be reliable. The PSCR stated that ‘the updated MAIC matched the most important prognostic factors to maintain a reasonable sample size’ and that the p-value for interaction test indicates many of the aforementioned unmatched variables (age, gender, 17p deletion, complex karyotype and CIRS score), are unlikely to be treatment effect modifiers. However, the ESC considered that these may be important prognostic variables in CLL, and as such the results of the MAICs may not be reliable. The pre-PBAC response stated, “The MAIC considered all of the latest available data and matched the most important prognostic factors to maintain a reasonable sample size”.
- 6.40 Summary results of the MAICs of progression-free survival and overall survival, based on a median follow-up of 46.9 months in the ELEVATE TN trial and 39.6 months in the CLL-14 trial, are presented in Table 9.

**Table 9: Results of the updated matching adjusted indirect comparisons for acalabrutinib +/- obinutuzumab versus venetoclax + obinutuzumab**

	ACAL + OBI vs VEN + OBI	ACAL vs VEN + OBI
Patients in the acalabrutinib +/- obinutuzumab arm of ELEVATE-TN	179	179
Patients included in MAIC prior to matching <sup>a</sup>	172	176
Effective sample size after matching	104	96
<b>Progression free survival: HR (95% CI)</b>		
Prior to MAIC adjustment (naïve comparison)	0.46 (0.26, 0.79)	0.81 (0.50, 1.29)
After MAIC adjustment	0.38 (0.20, 0.73)	0.96 (0.56, 1.65)
<b>Overall survival: HR (95% CI)</b>		
Prior to MAIC adjustment (naïve comparison)	0.41 (0.20, 0.85)	0.77 (0.42, 1.38)
After MAIC adjustment	0.43 (0.19, 0.99)	0.99 (0.51, 1.91)

Source: Table 2.76 of the resubmission.

ACAL = acalabrutinib, CI = confidence interval, HR = hazard ratio, MAIC = matching-adjusted indirect comparison, OBI = obinutuzumab, VEN = venetoclax

<sup>a</sup> Seven patients in the acalabrutinib + obinutuzumab arm and 3 patients in the acalabrutinib monotherapy arm were excluded due to missing baseline characteristic data

The variables that were matched in the MAIC analysis were: 11q deletion, TP53 mutation, ECOG status, IGHV mutation, creatinine clearance,  $\beta$ 2 microglobulin and CLL-IPI risk group.

- 6.41 For the comparison of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab, point estimates for progression-free survival and overall survival favoured acalabrutinib + obinutuzumab before and after matching, and the differences were statistically significant.
- 6.42 For the comparison of acalabrutinib monotherapy versus venetoclax + obinutuzumab, point estimates for progression-free survival and overall survival favoured acalabrutinib before and after matching, but the differences were not statistically significant.
- 6.43 The evaluation and the ESC considered that the results should be interpreted with caution due to the inadequate matching of prognostic variables in the analysis and the post hoc nature of the analysis.

### Comparative harms

- 6.44 Safety outcomes for the ELEVATE-TN trial at the October 2021 data cut (median follow-up of 58.2 months) are presented in Table 10. Available results for the October 2021 data cut were limited to adverse events with an incidence of  $\geq 30\%$ , and adverse events of clinical interest.

**Table 10: Summary of adverse events for the ELEVATE-TN trial at the October 2021 data cut (median follow-up of 58.2 months)**

	ACAL + OBI (N=178)		ACAL (N=179)		CHL + OBI (N=169)	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
<b>Any AE incidence <math>\geq 30\%</math>, n (%)</b>						
Diarrhoea	77 (43.3)	10 (5.6)	76 (42.5)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)	20 (11.8)	0
Arthralgia	60 (33.7)	4 (2.2)	47 (26.3)	2 (1.1)	10 (5.9)	2 (1.2)
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	77 (45.6)	71 (42.0)
Nausea	44 (24.7)	0	44 (24.6)	0	53 (31.4)	0
Infusion-related reaction	26 (14.6)	5 (2.8)	1 (0.6)	0	69 (40.8)	10 (5.9)
<b>AEs of clinical interest, n (%)</b>						
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
- Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
- Major bleeding	12 (6.7)	8 (4.5)	8 (4.5)	6 (3.4)	2 (1.2)	0
Infections	140 (78.7)	50 (28.1)	135 (75.4)	35 (19.6)	75 (44.4)	14 (8.3)
Second primary malignancy	31 (17.4)	14 (7.9)	27 (15.1)	7 (3.9)	7 (4.1)	3 (1.8)
- Excluding non-melanoma skin	17 (9.6)	12 (6.7)	13 (7.3)	5 (2.8)	3 (1.8)	2 (1.2)

Source: Table 2.54 of the submission; Table 1, of Sharman et al., 2022 (poster); Sharman et al., 2022 (abstract).

ACAL = acalabrutinib, AE = adverse event, ALT = alanine aminotransferase, CHL = chlorambucil, OBI = obinutuzumab

- 6.45 At a median follow-up of 58.2 months, atrial fibrillation was reported in 6.2% of patients in the acalabrutinib + obinutuzumab arm, 7.3% of patients in the acalabrutinib monotherapy arm, and 0.6% of patients in the chlorambucil + obinutuzumab arm. Major bleeding was reported in 6.7% of patients in the acalabrutinib + obinutuzumab arm, 4.5% of patients in the acalabrutinib arm, 1.2% of patients in the chlorambucil + obinutuzumab arm.

- 6.46 The ESC noted that the incidence of infusion-related reactions was lower in the acalabrutinib + obinutuzumab arm than in the chlorambucil + obinutuzumab arm (14.6% versus 40.8%, respectively for any grade infusion-related reactions), despite both regimens including the same injectable therapy (obinutuzumab) and despite exposure to obinutuzumab being similar across the two arms (CSR). It was unclear what premedications were administered prior to obinutuzumab in the trial, but it was noted that obinutuzumab was commenced in Cycle 1 (Day 1) in the chlorambucil + obinutuzumab arm but in Cycle 2 (Day 1) in the acalabrutinib + obinutuzumab arm. The ESC considered that it was unclear why the incidence of infusion-related reactions was reported to be lower in the acalabrutinib + obinutuzumab arm. The sponsor was requested to address this in its pre-PBAC response. In particular, the ESC requested that the sponsor address: (a) the rationale for the difference in infusion-related reactions between the two obinutuzumab arms; and (b) outline the pre-medications given in each arm, and any differences in pre-medications between arms. This issue was not addressed in the pre-PBAC response.
- 6.47 At the September 2020 data cut (median follow-up 46.9 months), serious adverse events were higher in the acalabrutinib + obinutuzumab (48%) and acalabrutinib monotherapy (39%) arms, compared to the chlorambucil + obinutuzumab arm (22%). Grade  $\geq 3$  adverse events were higher in the acalabrutinib + obinutuzumab (74%) and chlorambucil + obinutuzumab arms (69%) compared to the acalabrutinib monotherapy arm (52%).
- 6.48 The ESC noted that the number of hospitalisations per person-year was lower in the acalabrutinib + obinutuzumab arm than in the chlorambucil + obinutuzumab arm (0.294 versus 0.335, respectively) at the February 2019 data cut (Table 29 of the CSR).

### **Matching-adjusted indirect comparisons**

- 6.49 The resubmission presented MAICs of acalabrutinib + obinutuzumab and acalabrutinib monotherapy versus venetoclax + obinutuzumab for selected Grade 3-4 adverse events, based on the results of the ELEVATE-TN (median follow-up 46.9 months) and CLL-14 trials (median follow-up 39.6 months), as shown in Table 11.

**Table 11: Results for the MAIC of Grade 3-4 adverse events for acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab**

Grade 3-4 adverse events	Unadjusted		MAIC adjusted		
	ACAL + OBI (N=172) <sup>a</sup>	VEN + OBI (N=216)	ACAL + OBI (ESS=104)	VEN + OBI (N=216)	RD (95% CI)
Anaemia	NR	8.0%	6.0%	8.0%	-2.0 (-7.4, 3.3)
Diarrhoea	NR	3.8%	3.5%	3.8%	-0.3 (-4.1, 3.5)
Febrile neutropenia	NR	5.2%	3.3%	5.2%	-1.9 (-6.4, 2.5)
Infusion-related reaction	NR	9.0%	1.4%	9.0%	<b>-7.6 (-11.8, -3.4)</b>
Leukopenia	NR	2.4%	0.2%	2.4%	<b>-2.2 (-4.3, -0.1)</b>
Neutropenia	NR	52.8%	29.1%	52.8%	<b>-23.7 (-34.5, -12.8)</b>
Non-melanoma skin cancer	NR	8.0%	1.3%	8.0%	<b>-6.7 (-10.7, -2.7)</b>
Pneumonia	NR	5.7%	7.3%	5.7%	1.6 (-4.7, 8.0)
Secondary primary malignancy <sup>b</sup>	NR	9.0%	5.3%	9.0%	-3.7 (-10.0, 2.6)
Thrombocytopenia	NR	13.7%	9.6%	13.7%	-4.1 (-11.2, 3.1)
Tumour lysis syndrome	NR	1.4%	1.4%	1.4%	0 (-2.4, 2.4)

Source: Table 2.80; Slide 25 of Attachment 2L of the resubmission.

ACAL = acalabrutinib, CI = confidence interval, ESS = effective sample size, MAIC = matching adjusted indirect comparison, OBI = obinutuzumab, RD = risk difference, SPM, secondary primary malignancy, VEN = venetoclax

<sup>a</sup> Differs from ELEVATE-TN ITT due to removal of patients with incomplete baseline data.

<sup>b</sup> Excluding non-melanoma skin cancer.

Bolded results indicate statistically significant difference

- 6.50 The results should be interpreted with caution due to inadequate justification for the application of the MAIC methodology to specific adverse events (e.g., specific adverse events that may have been of interest were not included such as atrial fibrillation, hypertension and bleeding), the limited matching of prognostic variables and differences in follow-up durations in the data-cuts used.
- 6.51 After MAIC adjustment in the comparison of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab, there were statistically significant differences favouring acalabrutinib + obinutuzumab for Grade 3-4 infusion-related reactions, leukopenia, neutropenia and non-melanoma skin cancer. The ESC considered that it was unclear why the incidence of infusion-related reactions was reported to be lower with acalabrutinib + obinutuzumab than venetoclax + obinutuzumab, given both regimens include the same injectable therapy (obinutuzumab).
- 6.52 After MAIC adjustment in the comparison of acalabrutinib monotherapy versus venetoclax + obinutuzumab, there were statistically significant differences favouring acalabrutinib for Grade 3-4 febrile neutropenia, infusion-related reactions, leukopenia, neutropenia, non-melanoma skin cancer, secondary primary malignancy and thrombocytopenia.

### **Benefits/harms**

- 6.53 On the basis of a naïve comparison of acalabrutinib + obinutuzumab (ELEVATE-TN trial; median follow-up 58.2 months) and venetoclax + obinutuzumab (CLL-14 trial; median

follow-up 65.4 months), for every 100 patients treated with acalabrutinib + obinutuzumab in comparison with venetoclax + obinutuzumab:

- Approximately 21 additional patients will remain free from progression at 60 months.
- Approximately 8 additional patients will remain alive at 60 months.

6.54 On the basis of a naïve comparison of acalabrutinib + obinutuzumab (ELEVATE-TN trial; median follow-up 46.9 months) and venetoclax + obinutuzumab (median follow-up 39.6 months), for every 100 patients treated with acalabrutinib + obinutuzumab in comparison with venetoclax + obinutuzumab:

- Approximately 24 fewer patients will experience life-threatening or severe neutropenia.

6.55 The PBAC considered that these estimates were not reliable given the issues with the underlying clinical data (refer to paragraph 7.7).

### ***Clinical claim***

6.56 The resubmission described acalabrutinib + obinutuzumab as superior in terms of effectiveness and safety compared to venetoclax + obinutuzumab, in patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy.

6.57 The evaluation and the ESC considered that the therapeutic conclusion presented in the resubmission was partially supported:

- Based on a naïve comparison of results for the ELEVATE-TN and CLL-14 trials, the proportion of patients remaining free from disease progression at 60 months was numerically higher for acalabrutinib + obinutuzumab compared to venetoclax + obinutuzumab (84% versus 63%). The hazard ratio for the comparison of acalabrutinib + obinutuzumab and venetoclax + obinutuzumab favoured acalabrutinib + obinutuzumab and was statistically significant before and after matching in the MAIC analysis.
- Based on a naïve comparison of results for the ELEVATE-TN and CLL-14 trials, the proportion of patients remaining alive at 60 months was numerically higher for acalabrutinib + obinutuzumab compared to venetoclax + obinutuzumab (90% versus 82%). The hazard ratio for the comparison of acalabrutinib + obinutuzumab and venetoclax + obinutuzumab favoured acalabrutinib + obinutuzumab and was statistically significant before and after matching in the MAIC analysis. However, the ESC considered that the overall survival results were difficult to interpret due to the subsequent lines of effective therapy available in the context of the low-grade nature of CLL.
- The results of the naïve comparisons should be interpreted with caution due to differences in eligibility criteria between the ELEVATE-TN and CLL-14 trials and differences in patient characteristics between the trials (including median age and

the proportion with a CIRS score >6). Key patient characteristics data for the CLL-14 trial (including bulky disease and Rai stage) was not available.

- Results of the updated unanchored MAICs did not appear to be reliable as they did not adequately account for differences in eligibility criteria between the ELEVATE-TN and CLL-14 trials, or match for potentially important prognostic variables.
- There were differences between the clinical criteria included in the proposed restriction and the eligibility criteria for the ELEVATE-TN trial that may affect the applicability of the results to the PBS population. As outlined in Paragraph 3.4, the proposed restriction requires patients to have a CIRS score >6 or a creatinine clearance <70 mL/min, whereas patients recruited for the ELEVATE-TN trial were only required to meet the CIRS score/creatinine criteria if they were aged <65 years. The proportion of patients in the overall ELEVATE-TN trial population who would meet the proposed PBS criteria was not presented in the resubmission or in the PSCR. Based on the restriction proposed in the resubmission, the ESC considered that patients in the PBS population would be likely to have a higher burden of comorbidities compared to patients in the ELEVATE-TN trial, which may translate into differences in outcomes, particularly in terms of safety.
- Comparison of safety outcomes was constrained by the limited reporting of safety outcomes for the ELEVATE-TN and CLL-14 trials in publications reporting extended follow-up and differences in follow-up durations between the ELEVATE-TN and CLL-14 trials in the data-cuts used.

6.58 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data and that a claim of non-inferiority of acalabrutinib + obinutuzumab to venetoclax + obinutuzumab would be more appropriate.

6.59 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

### ***Economic analysis***

6.60 The resubmission presented a modelled economic evaluation of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab, in patients with previously untreated CLL/SLL who are unsuitable for treatment with fludarabine-based chemoimmunotherapy. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.61 A partitioned survival design, using extrapolated progression-free survival, time to next anti-leukaemic treatment, and overall survival data, was used to distribute patients between model health states. The area below the progression-free survival curve was used to estimate the proportion of patients in the first-line progression-free health state; the area between the progression-free survival and the time to next treatment curve was used to estimate the proportion of patients in the first-line progressed disease (progressed but well) health state; the area between the time to next treatment and overall survival curves was used to estimate the proportion of patients in the relapsed/refractory disease health state; and the area above the

overall survival curve was used to estimate the proportion of patients in the dead state.

6.62 The resubmission stated that the model structure was based on the model included in the July 2020 venetoclax + obinutuzumab resubmission. The model included in the November 2021 acalabrutinib resubmission was a partitioned survival model with three health states (progression-free, progressed disease and dead).

**Table 12: Key components of the economic evaluation**

Component	Summary
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	Quality-adjusted life years; progression-free life years; life years gained.
Time horizon	15 years in the model base case versus a median follow-up of 46.9 months in the ELEVATE-TN trial. <sup>a</sup>
Methods used to generate results	Partitioned survival analysis
Health states	First-line progression-free; first-line progressed disease; relapsed/refractory disease; dead.
Treatments	Sequential treatment with acalabrutinib + obinutuzumab followed by venetoclax + rituximab (90%) or idelalisib + rituximab (10%); versus sequential treatment with venetoclax + obinutuzumab followed by ibrutinib monotherapy (100%).
Cycle length	1 month
Allocation to health states	Kaplan-Meier estimates of progression-free survival, overall survival and time to next treatment for the acalabrutinib + obinutuzumab arm derived from the ELEVATE-TN trial and extrapolated using parametric functions (PFS: exponential function; OS: lognormal function; TTNT: exponential function).  Kaplan-Meier estimates of progression-free survival and overall survival for the venetoclax + obinutuzumab arm derived from indirect comparisons of the ELEVATE-TN and CLL-14 trials (MAICs for PFS and OS; Bucher method indirect comparison for TTNT).
Health state utility values	Based on health state utilities included in the July 2020 venetoclax resubmission: - First-line progression-free: 0.82 - First-line progressed disease: 0.776 - Relapsed/refractory disease: 0.66
Health resource use and costs	Treatment costs associated with first-line (acalabrutinib + obinutuzumab and venetoclax + obinutuzumab) and second-line treatments (ibrutinib, venetoclax + rituximab and idelalisib + rituximab).  Health state costs based on costs included in the July 2020 venetoclax resubmission.  Costs associated with selected adverse events with a statistically significant difference between acalabrutinib + obinutuzumab in the MAIC, and selected adverse events reported for second-line treatments.  Tumour lysis syndrome prophylaxis costs for venetoclax based on tumour lysis syndrome monitoring schedule outlined in the venetoclax product information.  Palliative care costs based on estimate reported by Kardamanidis et al. (2007).

Source: Section 3 of the resubmission.

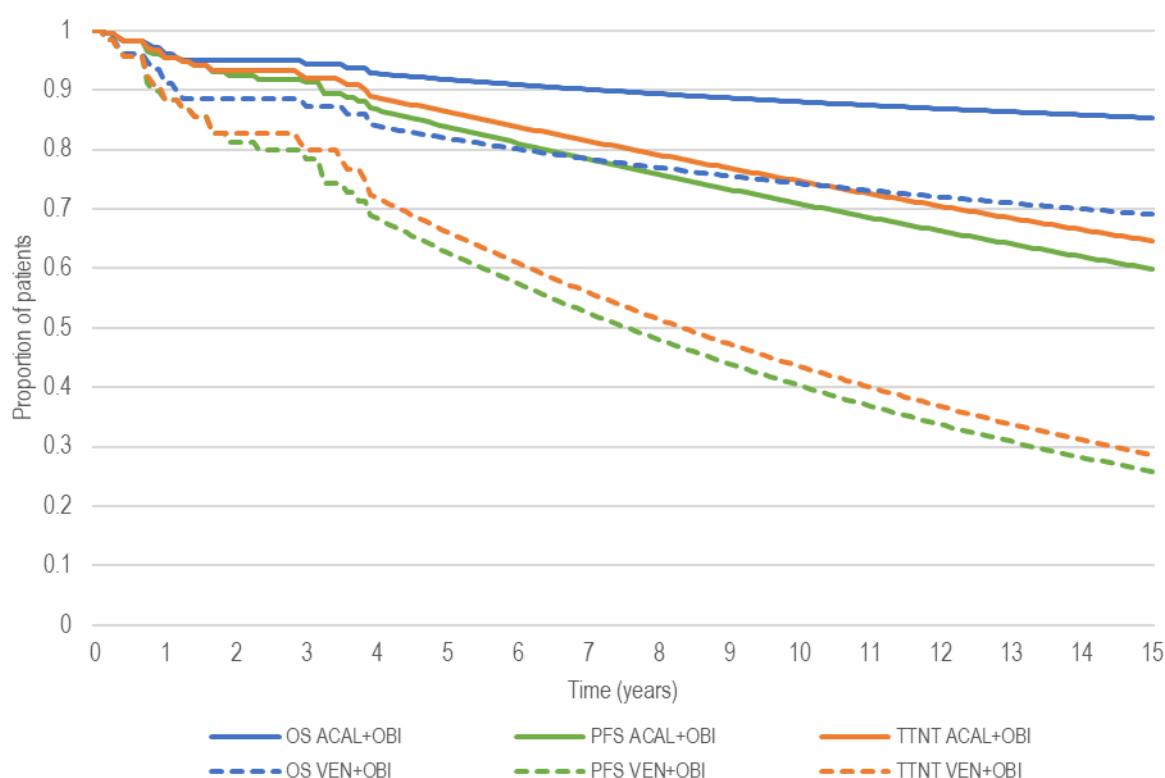
MAIC = matching adjusted indirect comparison, PFS = progression-free survival, OS = overall survival, TTNT = time to next treatment

<sup>a</sup> Progression-free survival, overall survival and time to next data used in the model were based on the September 2020 data cut.

6.63 Progression-free survival, overall survival and time to next treatment for the acalabrutinib + obinutuzumab arm of the ELEVATE-TN trial were based on Kaplan-Meier survival curves from the ELEVATE-TN trial at a median duration of follow-up of 46.9 months, extrapolated to 15 years using parametric functions.

- 6.64 Progression-free survival and overall survival curves for venetoclax + obinutuzumab were derived from the extrapolated acalabrutinib + obinutuzumab curves using the hazard ratio derived from the results of the MAIC analyses. Time to next treatment curves for venetoclax + obinutuzumab were derived from the extrapolated time to next treatment curve for acalabrutinib + obinutuzumab using a hazard ratio derived from the results of a Bucher method indirect comparison.
- 6.65 A comparison of the modelled overall survival, progression-free survival and time to next treatment for acalabrutinib + obinutuzumab and venetoclax + obinutuzumab is presented in Figure 6.

**Figure 6: Comparison of modelled overall survival, progression-free survival and time to next treatment for the acalabrutinib + obinutuzumab and venetoclax + obinutuzumab arms**



Source: Compiled using the 'Section 3 CEA model' Excel Workbook.

ACAL = acalabrutinib, OBI = obinutuzumab, OS = overall survival, PFS = progression-free survival, TTNT = time to next treatment, VEN = venetoclax

Note: Plot excludes background population mortality adjustment (applied in the model from 48 months).

- 6.66 The application of a constant hazard ratio to the acalabrutinib + obinutuzumab progression-free survival, overall survival and time to next treatment data to derive the venetoclax + obinutuzumab curves may not be reasonable, given it resulted in increasing differences between acalabrutinib + obinutuzumab and venetoclax + obinutuzumab in progression-free survival, overall survival and time to next treatment over time, and there was a lack of longer-term data to validate these assumptions.
- 6.67 The ESC noted that the model presented in the pre-PBAC response for venetoclax + obinutuzumab applied risk convergence from five years (paragraph 5.19, venetoclax

Public Summary Document (PSD), July 2020 PBAC Meeting), and considered that this may be a potential method to address the aforementioned issues with the application of the constant hazard ratio.

- 6.68 Modelled circumstances of use for first-line therapies were based on the treatment regimens used in the acalabrutinib + obinutuzumab arm of the ELEVATE-TN trial, and the venetoclax + obinutuzumab arm of the CLL-14 trial. The duration of first-line treatment with acalabrutinib + obinutuzumab arm was estimated from the extrapolated time to treatment discontinuation curve for the acalabrutinib + obinutuzumab arm of the ELEVATE-TN trial. The duration of first-line venetoclax treatment was based on the mean duration of treatment reported in the July 2020 venetoclax Public Summary Document (288 days). Patients in the acalabrutinib + obinutuzumab and venetoclax + obinutuzumab arms were assumed to receive a total of 8 infusions of obinutuzumab over 6 cycles.
- 6.69 The resubmission noted that, given the partitioned survival approach used in the model, treatment effectiveness reflected the first- and subsequent-line treatments used by patients in the ELEVATE-TN and CLL-14 trials. In order to estimate drug costs and adverse event management costs associated with second-line treatments used by patients in the PBS population, the resubmission assumed that second-line therapy for patients treated with acalabrutinib + obinutuzumab would consist of venetoclax + rituximab (90%) and idelalisib + rituximab (10%), and second-line therapy for patients treated with venetoclax + obinutuzumab would consist of ibrutinib.
- 6.70 In the resubmission, the cost of acalabrutinib in the model was assumed to be nil beyond 60 months to reflect the 60-month treatment cap in the proposed RSA. The PBAC had previously considered that the use of a treatment cap to achieve cost-effectiveness was not a robust approach, and that the ICER would be much higher if patient numbers used to inform the caps were lower than estimated (paragraph 7.10, acalabrutinib, Public Summary Document, November 2021 PBAC meeting). As such the ESC considered the exclusion of acalabrutinib drug costs beyond 60 months in the base case of the model was not reasonable. The pre-PBAC response withdrew this proposal, stating “As a result, costs for acalabrutinib treatment on the PBS would continue beyond 60 months in the economic model, substantially increasing the ICER if no other model variables change. It is noted a lower acalabrutinib price would be required to deliver an acceptable ICER”.
- 6.71 Tumour lysis syndrome costs were included for venetoclax in the first and second-line setting. The November 2021 resubmission assumed that treatment with obinutuzumab was associated with tumour lysis syndrome prophylaxis costs (based on the average cost per patient of \$1,222 estimated for venetoclax + obinutuzumab in the July 2020 venetoclax resubmission). The exclusion of tumour lysis syndrome costs for obinutuzumab is likely to favour the acalabrutinib + obinutuzumab arm given that the costs associated with tumour lysis syndrome monitoring/prophylaxis are already included for the venetoclax + obinutuzumab arm. The ESC noted the ICER

increased by 7% when tumour lysis syndrome prophylaxis costs in the first-line setting were removed.

- 6.72 The evaluation considered that the assumed cost and utility for the relapsed/refractory health state may not adequately reflect the cost and quality of life experienced by patients with CLL over time, given multiple lines of subsequent therapy, and periods of disease remission, however the ESC considered that health state costs were unlikely to be a key driver of the model (e.g., the exclusion of all health state costs had less than 10% impact on the ICER).
- 6.73 Key drivers of the economic model are summarised in Table 13.

**Table 13: Key drivers of the model**

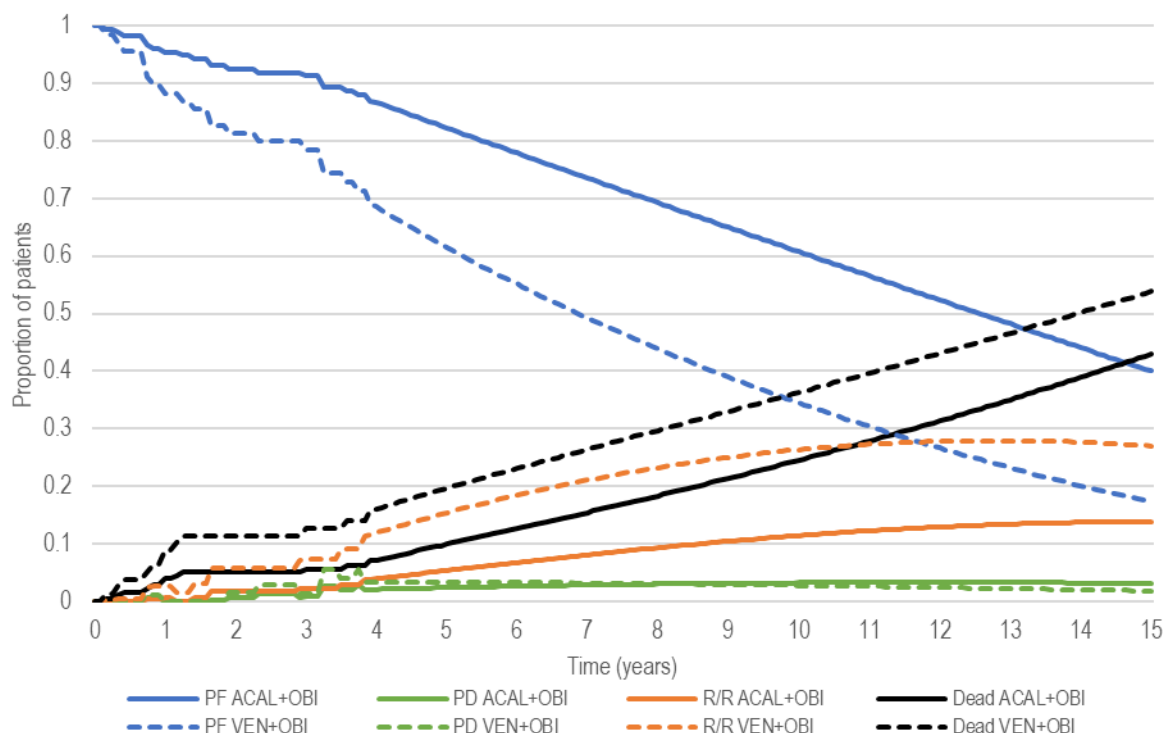
Description	Method/Value	Impact
Time horizon	<p>The base case assumed a 15-year time horizon with a one-month cycle length. The PBAC previously considered that a 10-year time horizon would be more reasonable than a 15-year horizon, as it would be consistent with previous decisions in the first-line CLL/SLL setting and given that a longer extrapolation would be subject to considerable uncertainty (paragraph 7.10, acalabrutinib, Public Summary Document, November 2021 PBAC meeting).</p> <p>The PSCR maintained that a 15-year time horizon was appropriate, given that 90% of patients receiving acalabrutinib + obinutuzumab were alive at 5 years in the longer-term follow-up data, and given that effective therapies are available in the relapsed/refractory setting. However, the ESC considered that the extrapolation of outcomes to 15 years is associated with substantial uncertainty and that a 10-year time horizon would be more appropriate and consistent with previous decisions in the unfit population in the first-line CLL/SLL setting. The pre-PBAC response argued that while shorter time horizons had been applied in submissions for other CLL therapies, these therapies were fixed duration, whereas acalabrutinib is a treat to progression regimen.</p>	Moderate, favours acalabrutinib
Acalabrutinib + obinutuzumab survival extrapolations	<p>Progression-free survival and overall survival data for acalabrutinib + obinutuzumab corresponding to a median duration of follow-up of 46.9 months were extrapolated to 15 years using parametric functions. The extrapolated survival data was considered uncertain due to the lack of available clinical evidence to validate the longer-term survival assumptions.</p>	Moderate, favours acalabrutinib
Venetoclax + obinutuzumab survival	<p>Progression-free survival and overall survival estimates for venetoclax + obinutuzumab were derived from the extrapolated progression-free survival and overall survival for acalabrutinib + obinutuzumab based on the hazard ratio derived from the MAIC. The application of a constant hazard ratio to the extrapolated acalabrutinib + obinutuzumab progression-free survival, overall survival curves to derive the venetoclax + obinutuzumab curves may not be reasonable, given that it resulted in increasing differences between acalabrutinib + obinutuzumab and venetoclax + obinutuzumab over time. There was a lack of longer-term data to validate these increasing differences.</p>	High, favours acalabrutinib
Partitioned survival analysis	<p>A partitioned survival design, using the overall survival and progression-free survival results from the ELEVATE-TN trial, was implemented to distribute patients between model health states. The assumed cost and utility for the relapsed/refractory health state may not adequately reflect the cost and quality of life experienced by patients with CLL over time, given multiple lines of subsequent therapy, and periods of disease remission.</p>	High, favours acalabrutinib
Subsequent treatment costs	<p>Subsequent therapy costs were derived based on the assumption that patients in the acalabrutinib arm would receive subsequent treatment with venetoclax + obinutuzumab (90%) or idelalisib with rituximab (10%), and patients in the venetoclax + obinutuzumab arm would receive subsequent treatment with ibrutinib monotherapy. While the intention of this assumption was to model costs for the PBS population based on available PBS-listed treatments, this resulted in a mismatch between assumed use and actual use in the ELEVATE-TN and CLL-14 trials.</p> <p>The resubmission estimated the impact of risk-sharing arrangements for idelalisib and ibrutinib by assuming maximum treatment duration caps of 12 and 44 months for idelalisib and ibrutinib, respectively. The assumed maximum treatment caps may not reflect the actual risk-sharing arrangements in place</p>	Unclear impact

Source: Constructed during the evaluation.

PSCR = Pre-Sub-Committee Response

6.74 Model traces for the acalabrutinib + obinutuzumab and venetoclax + obinutuzumab arms are presented in Figure 7.

Figure 7: Model traces for the acalabrutinib + obinutuzumab and venetoclax + obinutuzumab arms



Source: Constructed during the evaluation using the 'Section 3 CEA model' Excel workbook.

ACAL, acalabrutinib, OBI = obinutuzumab, PD, progressive disease, PF = progression-free, R/R, relapsed/refractory, VEN = venetoclax

Note: Half cycle correction not included in model traces.

6.75 The model traces indicated that approximately 57% of patients in the acalabrutinib + obinutuzumab arm were alive at 15 years, with approximately 40% of patients remaining progression-free.

6.76 The results of the modelled economic evaluation using the resubmission’s estimated effective prices for venetoclax, obinutuzumab, ibrutinib and idelalisib are summarised in Table 14.

Table 14: Results of the economic evaluation

Component	Acalabrutinib + obinutuzumab	Venetoclax + obinutuzumab	Increment
<b>Base case: with RSA rebates applied (i.e., no acalabrutinib drug costs applied after 60 months)</b>			
Costs	\$█	\$█	\$█
QALYs	7.372	6.386	0.986
LYs	9.150	8.158	0.992
<b>Incremental cost per QALY gained</b>			<b>\$█<sup>1</sup></b>
<b>Without RSA rebates applied</b>			
Costs	\$█	\$█	\$█
QALYs	7.372	6.386	0.986
<b>Incremental cost per QALY gained</b>			<b>\$█<sup>2</sup></b>

Source: Table 3.30 of the resubmission.

QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

<sup>1</sup>\$45,000 to < \$55,000

<sup>2</sup>\$155,000 to < \$255,000

- 6.77 Based on the economic model, treatment with acalabrutinib + obinutuzumab was associated with an incremental cost per QALY gained of \$45,000 to < \$55,000 compared to venetoclax + obinutuzumab with the proposed RSA rebates applied, and \$155,000 to < \$255,000 per QALY without the rebates applied. The ESC noted that, without the RSA rebates applied, a 46% price reduction would be required to achieve the ICER of \$45,000 to < \$55,000 per QALY. The pre-PBAC response stated that it withdrew the RSA proposal and noted this would substantially increase the ICER if no other model variables change.
- 6.78 The difference in total cost between treatment arms was primarily driven by first-line treatment costs, which was partly offset by second-line treatment costs, disease monitoring costs and first-line tumour lysis syndrome monitoring costs.
- 6.79 The difference in health outcomes between treatment arms was driven the higher number of life years for the acalabrutinib + obinutuzumab arm, and by the differences in time spent in the first-line progression-free and relapsed/refractory health states.
- 6.80 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in Table 15 (based on the resubmission’s model with RSA caps applied).

Table 15: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
<b>Base case</b>	\$█	<b>0.986</b>	\$█	-
<b>Time horizon (base case 15 years)</b>				
5 years	\$█	0.262	\$█	422%
10 years (A)	\$█	0.657	\$█	63%
<b>PFS extrapolation for acalabrutinib + obinutuzumab (base case: exponential function)<sup>a</sup></b>				
Weibull	\$█	0.973	\$█	7%
Gompertz	\$█	0.948	\$█	20%
<b>OS extrapolation for acalabrutinib + obinutuzumab (base case: log-normal)</b>				
Gompertz	\$█	0.870	\$█	12%
Weibull	\$█	1.014	\$█	-2%
Exponential	\$█	1.116	\$█	-10%
<b>Time to treatment discontinuation extrapolation for acalabrutinib + obinutuzumab (base case: exponential)</b>				
Log-normal	\$█	0.99	\$█	1%
<b>PFS hazard ratio for venetoclax + obinutuzumab (base case: 0.38)</b>				
Hazard ratio 0.20 (lower 95% CI of MAIC)	\$█	1.076	\$█	-11%
Hazard ratio 0.73 (upper 95% CI of MAIC)	\$█	0.770	\$█	88%
Hazard ratio 1.0	\$█	0.681	\$█	143%
<b>OS hazard ratio for venetoclax + obinutuzumab (base case: 0.43)</b>				
Hazard ratio 0.19 (lower 95% CI of MAIC)	\$█	2.162	\$█	-47%
Hazard ratio 0.99 (upper 95% CI of MAIC)	\$█	0.336	\$█	166%
Hazard ratio 1.0	\$█	0.331	\$█	170%
<b>TTNT hazard ratio for venetoclax + obinutuzumab (base case: 0.346)</b>				
Hazard ratio 0.275 (lower 95% CI of Bucher indirect)	\$█	1.013	\$█	-10%
Hazard ratio 0.435 (upper 95% CI of Bucher indirect)	\$█	0.929	\$█	25%
Hazard ratio 1.0	\$█	0.992	\$█	134%
<b>Survival curve convergence (base: no convergence; constant HR over 15 years for PFS, OS, TTNT)</b>				

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Analyses	Incremental cost	Incremental QALY	ICER	% change
PFS, OS, TTNT HRs converge between 5 years and 15 years	\$█	0.891	\$█ <sup>1</sup>	27%
PFS, OS, TTNT HRs converge between 5 years and 10 years (B)	\$█	0.846	\$█ <sup>2</sup>	41%
PFS, OS, TTNT curves converge linearly between 5 years and 15 years	\$█	0.548	\$█ <sup>3</sup>	165%
<b>All-cause mortality (base case: applied from 48 months)</b>				
All-cause mortality removed	\$█	1.118	\$█ <sup>4</sup>	-25%
<b>Treatment costs (base case: acalabrutinib – proposed effective DPMQ with 60-month cap; venetoclax – █% rebate to published DPMQ; obinutuzumab – █% rebate on published AEMP; ibrutinib – estimated effective DPMQ with 24-month cap; idelalisib – █% rebate on published AEMP with 12-month cap; rituximab – published DPMA)</b>				
Cycle cap of 48 months (cap proposed in November 2021 resubmission)	\$█	0.986	\$█ <sup>5</sup>	-45%
Remove cycle cap for ongoing second-line therapies (ibrutinib, idelalisib)	\$█	0.986	\$█ <sup>6</sup>	-9%
Remove dose intensity for acalabrutinib	\$█	0.986	\$█ <sup>1</sup>	16%
<b>Proportion of acalabrutinib + obinutuzumab patients treated with second line venetoclax + rituximab (base case: 90%)</b>				
100%	\$█	0.986	\$█ <sup>1</sup>	6%
80%	\$█	0.986	\$█ <sup>6</sup>	-6%
<b>Utilities (base case: first-line progression-free 0.82; first-line progressed disease decrement of 0.044; relapsed/refractory disease 0.66)</b>				
First line progression-free increased to 0.87	\$█	1.089	\$█ <sup>6</sup>	-9%
First-line progression-free decreased to 0.77	\$█	0.883	\$█ <sup>1</sup>	12%
Relapsed/refractory disease increased to 0.71	\$█	0.932	\$█ <sup>1</sup>	6%
Relapsed/refractory disease decreased to 0.61	\$█	1.039	\$█ <sup>6</sup>	-5%
<b>Other costs (base case: health state, adverse event and TLS prophylaxis costs included)</b>				
Health state costs removed	\$█	0.986	\$█ <sup>1</sup>	9%
Adverse event costs removed	\$█	0.986	\$█ <sup>1</sup>	4%
First-line TLS prophylaxis costs removed	\$█	0.986	\$█ <sup>1</sup>	7%
<b>Discount rate (base case: 5% for benefits and costs)</b>				
0% for costs and benefits	\$█	1.441	\$█ <sup>4</sup>	-29%
3.5% for costs and benefits	\$█	1.098	\$█ <sup>6</sup>	-9%
<b>Multivariate sensitivity analyses</b>				
<b>A + B</b> + no acalabrutinib RSA rebates applied (i.e., 10-year time horizon plus HRs converge between 5 and 10 years plus no RSA rebates for acalabrutinib)	\$█	0.618	\$█ <sup>7</sup>	331%
<b>A</b> + no acalabrutinib RSA rebates applied (i.e., 10-year time horizon plus no RSA rebates for acalabrutinib)	\$█	0.657	\$█ <sup>7</sup>	290%
<b>B</b> + no acalabrutinib RSA rebates applied (i.e., HRs converge between 5 and 10 years plus no RSA rebates for acalabrutinib)	\$█	0.846	\$█ <sup>7</sup>	301%

Source: Compiled using the 'Section 3 CEA model' Excel Workbook.

AEMP = approved ex-manufacturer price, CI = confidence interval, DPMA = dispensed price for maximum amount, DPMQ = dispensed price for maximum quantity, MAIC = matching adjusted indirect comparison, OS = overall survival, PFS = progression-free survival, TLS = tumour lysis syndrome, TTNT = time to next treatment

<sup>a</sup> Use of alternative PFS extrapolations in the model also resulted in corresponding changes to the selected time to treatment discontinuation and time to next treatment extrapolations to prevent curve crossing.

<sup>b</sup> In the relapsed/refractory setting, both ibrutinib and venetoclax+rituximab were assumed to have a 'subsidised treatment cap' of 22 months, resulting in mean durations of 19.5 months and 20 months, respectively.

<sup>c</sup> In the relapsed/refractory setting, both ibrutinib and venetoclax+rituximab were assumed to have a 'subsidised treatment cap' of 39 months, resulting in mean durations of 30.1 months and 30 months, respectively.

The redacted values correspond to the following ranges:

<sup>1</sup>\$55,000 to < \$75,000

<sup>2</sup>\$75,000 to < \$95,000

<sup>3</sup>\$135,000 to < \$155,000

<sup>4</sup>\$35,000 to < \$45,000

<sup>5</sup>\$25,000 to < \$35,000

<sup>6</sup>\$45,000 to < \$55,000

<sup>7</sup>\$155,000 to < \$255,000

- 6.81 The model was most sensitive to the choice of time horizon, the discount rate, the assumed hazard ratios for progression-free survival, overall survival and time to next treatment, and removal of the acalabrutinib cap at 60 months.
- 6.82 The ESC noted the results of a multivariate sensitivity analysis incorporating:
- a 10-year time horizon, and
  - convergence of PFS, OS, TTNT hazard ratios between 5 years and 10 years; and
  - without the RSA rebates for acalabrutinib (i.e., acalabrutinib drug costs were applied beyond 60 months)
  - increased the ICER from \$45,000 to < \$55,000 per QALY to \$155,000 to < \$255,000 per QALY.
- 6.83 The pre-PBAC response argued that the application of a shorter time horizon and convergence of hazard ratios, which had been applied in previous submissions of fixed duration regimens in first-line CLL, was inappropriate as acalabrutinib + obinutuzumab is a treat to progression regimen (e.g. 77% of patients remain on acalabrutinib treatment at 5 years).

### **Drug cost/patient/course**

- 6.84 Table 16 presents a comparison of drug costs for acalabrutinib + obinutuzumab and venetoclax + obinutuzumab included in the economic model and financial estimates. The estimated drug cost for acalabrutinib was \$| per patient per year. The resubmission estimated a maximum cost of \$| per patient for acalabrutinib based on the proposed risk-sharing arrangement cap of 60 months. The average cost per patient estimated in the economic model with the RSA was \$| (undiscounted) (average duration of treatment of 49.8 months), and without the RSA was \$| (undiscounted) (average duration of treatment of 104 months). The average cost per patient was substantially more for acalabrutinib + obinutuzumab than for venetoclax + obinutuzumab (\$| versus \$|, respectively, including obinutuzumab costs).
- 6.85 These results were based on the resubmission's estimates of the effective prices of other CLL therapies.

**Table 16: Drug cost per patient for proposed and comparator drugs**

	Clinical study	Economic model	Financial estimates
<b>Acalabrutinib + obinutuzumab</b>			
<b>ACALABRUTINIB</b>			
Cost per script (proposed DPMQ)	-	\$█	\$█
Adherence	Mean dose intensity (ELEVATE-TN): 94.6%	12.33 scripts (13.036 <sup>a</sup> scripts x 94.6% dose intensity)	12.34 scripts (13.044 <sup>a</sup> scripts x 94.6% dose intensity)
Cost per year	-	Year 1-5: \$█ Year 6+: \$█	\$█
Proportion of patients on treatment (persistence) <sup>b</sup>	Year 1: 85.6% <sup>c</sup> Year 2: 82.3% <sup>c</sup> Year 3: 77.9% <sup>c</sup> Year 4: 77.0% <sup>c</sup> Year 5: NA Year 6: NA	Year 1: 95.2% Year 2: 86.0% Year 3: 82.6% Year 4: 78.1% Year 5: 73.1% Year 6: 67.1%	Year 1: 100% Year 2: 93.61% Year 3: 87.63% Year 4: 82.03% Year 5: 76.79% Year 6: 0% <sup>d</sup>
Average cost per course of acalabrutinib	-	\$█ with RSA; \$█ without RSA undiscounted	\$█ with RSA
<b>OBINUTUZUMAB</b>			
Cost per script (estimated effective weighted DPMA)	-	\$ <sup>e</sup> █	\$ <sup>f</sup> █
Compliance	7.559 scripts/course <sup>g</sup>	8 scripts (based on 8 scripts x 100% dose intensity)	7.50 scripts (8.00 scripts x 93.8% dose intensity) <sup>h</sup>
Cost per course	-	\$█	\$█
<b>Venetoclax + obinutuzumab</b>			
<b>VENETOCLAX</b>			
Cost per script (estimated effective DPMQ)	-	Continuing pack: \$█	Starter pack: \$█ Continuing pack: \$█
Compliance	Mean treatment duration (CLL-14): 288.1 days	Starter pack: 0 scripts <sup>i</sup> Continuing pack: 9.61 scripts <sup>i</sup>	Starter pack: 1 script Continuing pack: 8.67 scripts
Cost per course	-	\$█	\$█
<b>OBINUTUZUMAB</b>			
Cost per script (estimated effective weighted DPMA)	-	\$ <sup>e</sup> █	\$ <sup>f</sup> █
Compliance	7.355 scripts/course	8 scripts (8 scripts x 100% dose intensity)	7.35 scripts (7.35 scripts x 100% dose intensity)
Cost per course	-	\$█	\$█

Source: Compiled using the 'Section 3 CEA model' and '4A\_Epidemiology Model' Excel workbooks.

<sup>a</sup> Calculated as 13.036 scripts based on 365 days per year (365/28) and 13.044 scripts based on 365.25 days per year (365.25/28).

<sup>b</sup> Average utilisation in each year of treatment.

<sup>c</sup> Based on Kaplan-Meier data for the ELEVATE-TN in the 'KM data' tab of the 'Section 3 CEA model' Excel workbook.

<sup>d</sup> Assumed no treated patients beyond Year 5 to reflect impact of the proposed risk-sharing arrangement.

<sup>e</sup> Estimated effective DPMA weighted based on a 49%/51% public/private hospital split.

<sup>f</sup> Estimated effective DPMA weighted based on a 28.4%/71.6% public/private hospital split.

<sup>g</sup> Mean cumulative dose reported in the acalabrutinib + obinutuzumab arm of the ELEVATE-TN trial divided by the recommended obinutuzumab dose (1,000 mg).

<sup>h</sup> The applied dose intensity for obinutuzumab when used with acalabrutinib (93.8%) was the dose intensity for the CHL + OBI arm of the ELEVATE-TN trial rather than ACAL + OBI arm (94.5%).

<sup>i</sup> Estimated based on mean venetoclax treatment duration of 288.1 days in the CLL-14 trial. The resubmission inappropriately assumed that all venetoclax scripts were continuing scripts, which overestimated the cost of venetoclax.

### Estimated PBS usage & financial implications

6.86 This resubmission was not considered by DUSC. The resubmission used a mixed epidemiological/market share approach to estimate the utilisation and financial impacts associated with the PBS listing of acalabrutinib + obinutuzumab for patients with previously untreated CLL/SLL who are unsuitable for treatment with fludarabine-based chemoimmunotherapy. No estimates for the number of grandfathered patients were provided in the resubmission.

6.87 The sources of data used in the financial estimates are presented in Table 17.

**Table 17: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Incident CLL patients	Incidence of 8.6/100,000 (crude rate; 2021 AIHW estimate) applied to ABS Australian population projections (Series B 3222.0).	The evaluation noted that the estimated crude incidence rates for CLL in the AIHW cancer data have been updated to 9.1/100,000, and 9.4/100,000 for 2021 and 2022 respectively. The AIHW data also suggests a trend towards increasing incidence over time. The resubmission did not account for patients with SLL. The PSCR updated the incidence rate to 9.4/100,000 in line with the most recent AIHW data.
Proportion initiating treatment	Assumed that 30% initiate treatment in year of diagnosis, and 7.5% initiate in years 2, 3, 4 and 5 following CLL diagnosis. Based on venetoclax PSD July 2020 (sponsor assumption).	Unchanged from the November 2021 resubmission. No additional justification provided.
Proportion of first-line eligible patients who are unsuitable for fludarabine-based chemoimmunotherapy	65%. Based on venetoclax PSD July 2020 (clinician advice).	Unchanged from the November 2021 resubmission. The PBAC considered that, in clinical practice, almost all patients would be considered to be unsuitable for fludarabine-based chemoimmunotherapy given FCR is poorly tolerated and associated with a risk of cytopenia and secondary malignancies.
Current market share of venetoclax + obinutuzumab	90%. Based on venetoclax PSD July 2020.	The evaluation and the ESC considered this assumption was uncertain. The resubmission did not account for potential substitution of acalabrutinib for chlorambucil + obinutuzumab.
Uptake/replacement rate of acalabrutinib + obinutuzumab for venetoclax + obinutuzumab	30% in Year 1 to 60% in Year 4 onwards. Sponsor assumption.	Uptake/replacement rates were considered uncertain. Acalabrutinib + obinutuzumab uptake rates may be higher than estimated in the resubmission due to longer progression-free survival for acalabrutinib + obinutuzumab compared to fixed duration venetoclax + obinutuzumab.
Choice of subsequent therapy	Assumed that patients treated with first-line ACAL + OBI will receive VEN + RIT (90%) or IDEL with RIT (10%). Assumed that patients treated with first-line venetoclax + obinutuzumab will receive IBR (85.2%) or ACAL (14.8%).	The assumptions were generally consistent with assumed subsequent treatments for the economic model.
First-line ACAL scripts per year	12.34. Based on the number of scripts required for a full year of treatment, multiplied by the relative dose intensity of co-administered ACAL in the ACAL + OBI arm of ELEVATE-TN (13.04; 94.6%).	It may not be reasonable to assume use in Australian clinical practice will be equivalent to use in the ELEVATE-TN trial.

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Parameter	Value applied and source	Comment
First-line OBI scripts (ACAL + OBI)	7.50. Based on the planned number of OBI administrations in the ELEVATE-TN trial adjusted for dose intensity (8 administrations; 93.8% dose intensity).	The applied dose intensity (93.8%) was the dose intensity for the CHL + OBI arm of the ELEVATE-TN trial rather than ACAL + OBI arm (94.5%).
Displaced first-line venetoclax scripts	Estimated displaced VEN scripts based on the decline of VEN + OBI scripts in proportion to the treatment uptake of ACAL + OBI. Average number of scripts per course of VEN when used in combination with OBI was 9.67 scripts (Table 7 venetoclax PSD July 2020).	The resubmission inappropriately included 13.04 starter pack scripts per patient rather than one. The estimated scripts per course was based on the mean treatment duration for venetoclax and did not appear to include adjustment for dose intensity. It may not be reasonable to include a dose intensity adjustment for acalabrutinib and not venetoclax.
First-line OBI scripts (VEN + OBI)	7.35. Based on the number of OBI scripts per course in the CLL-14 trial reported in Table 7 of the July 2020 venetoclax PSD.	The number of OBI administrations (7.35) was lower than assumed for patients treated with ACAL + OBI (7.50).
Drug prices	Venetoclax, acalabrutinib, obinutuzumab, idelalisib, and ibrutinib are subject to special pricing arrangements. The effective price of ibrutinib is known to the sponsor. Effective prices for obinutuzumab and idelalisib were estimated by assuming a 50% discount to their published ex-manufacturer prices. The effective price of venetoclax was estimated by assuming a 29.68% discount to the published ex-manufacturer prices.	

Source: Section 4 of the resubmission.

ABS = Australian Bureau of Statistics, ACAL = acalabrutinib, AIHW = Australian Institute of Health and Welfare CLL = chronic lymphocytic leukaemia, IBR = ibrutinib, IDEL= idelalisib, OBI = obinutuzumab, PFS = progression-free survival, PSCR = Pre-Sub-Committee Response, PSD = Public Summary Document, RIT = rituximab, R/R = relapsed/refractory, RSA = risk-sharing agreement, VEN = venetoclax

6.88 The estimated net cost to the PBS/RPBS of listing acalabrutinib + obinutuzumab is presented in Table 18 (based on the resubmission's estimates of the effective prices of other CLL therapies).

**Table 18: Estimated number of treated patients and the cost of acalabrutinib + obinutuzumab to the PBS/RPBS**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Total ACAL + OBI initiating patients</b>						
CLL incidence (8.6/100,000)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Total initiating patients	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Unfit for fludarabine (65%)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Market share of VEN + OBI (90%)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Uptake/replacement rate of ACAL + OBI for VEN + OBI	30%	40%	50%	60%	60%	60%
Number of patients electing treatment with ACAL + OBI	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Total ACAL scripts (13.04/year x 94.6% relative dose intensity)	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Total OBI scripts (17.39/year x 93.8% relative dose intensity)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Estimated financial implications of acalabrutinib + obinutuzumab</b>						
Total ACAL cost (\$█ per script) less copayments	\$█ <sup>6</sup>	\$█ <sup>7</sup>	\$█ <sup>8</sup>	\$█ <sup>9</sup>	\$█ <sup>10</sup>	\$█ <sup>11</sup>
Total OBI cost (\$█ per script) less copayments	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>
<b>Estimated financial implications for other first-line treatments</b>						
Net saving for displaced VEN	-\$█ <sup>12</sup>	-\$█ <sup>12</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>	-\$█ <sup>7</sup>
Net saving for displaced OBI	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>12</sup>
<b>Estimated financial implications for second-line treatments</b>						
Net saving for displaced IBR	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>12</sup>
Net saving for displaced ACAL	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>
Net cost of additional VEN	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>
Net cost of additional RIT	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>
Net cost of additional IDEL	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>
<b>Net financial implications of listing acalabrutinib + obinutuzumab</b>						
Net cost of ACAL + OBI	\$█ <sup>12</sup>	\$█ <sup>7</sup>	\$█ <sup>13</sup>	\$█ <sup>14</sup>	\$█ <sup>11</sup>	\$█ <sup>15</sup>
Net saving for other treatments	-\$█ <sup>12</sup>	-\$█ <sup>7</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>13</sup>	-\$█ <sup>13</sup>
<b>Net cost to PBS/RPBS</b>	-\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>12</sup>	\$█ <sup>7</sup>	\$█ <sup>13</sup>	\$█ <sup>13</sup>
Net cost to MBS	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>
<b>Net cost to PBS/RPBS/MBS</b>	-\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>12</sup>	\$█ <sup>7</sup>	\$█ <sup>13</sup>	\$█ <sup>13</sup>
<b>PSCR (increased the crude incidence rate from 8.6 to 9.4 per 100,000)</b>						
<b>Net cost to PBS/RPBS</b>	-\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>12</sup>	\$█ <sup>7</sup>	\$█ <sup>13</sup>	\$█ <sup>9</sup>
<b>Net cost to PBS/RPBS/MBS</b>	-\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>12</sup>	\$█ <sup>7</sup>	\$█ <sup>13</sup>	\$█ <sup>9</sup>
<b>November 2021 acalabrutinib submission</b>						
Net cost to PBS/RPBS/MBS	\$█ <sup>5</sup>	\$█ <sup>6</sup>	\$█ <sup>12</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>

Source: Compiled using the '4A\_Epidemiology Model' Excel workbook, Table 3 of PSCR (cell E25 was changed from 8.6 to 9.4 in '8. ABS population' worksheet).

ACAL = acalabrutinib, CHL = chlorambucil, CLL = chronic lymphocytic leukaemia, IBR = ibrutinib, IDEL = idelalisib, OBI = obinutuzumab, PSCR = Pre-Sub-Committee Response, RIT = rituximab, VEN = venetoclax  
Blue highlighted cells indicate July 2020 estimates.

The redacted values correspond to the following ranges:

- <sup>1</sup>500 to < 5,000
- <sup>2</sup>< 500
- <sup>3</sup>5,000 to < 10,000
- <sup>4</sup>10,000 to < 20,000
- <sup>5</sup>20,000 to < 30,000

<sup>6</sup>\$0 to < \$10 million

<sup>7</sup>\$20 million to < \$30 million

<sup>8</sup>\$30 million to < \$40 million

<sup>9</sup>\$50 million to < \$60 million

<sup>10</sup>\$70 million to < \$80 million

<sup>11</sup>\$80 million to < \$90 million

<sup>12</sup>\$10 million to < \$20 million

<sup>13</sup>\$40 million to < \$50 million

<sup>14</sup>\$60 million to < \$70 million

<sup>15</sup>\$90 million to < \$100 million

6.89 The PSCR estimated a net cost to the PBS/RPBS/MBS comprising a saving of \$0 to < \$10 million in Year 1 of listing, increasing to a cost of \$50 million to < \$60 million in Year 6, an estimated net cost of \$100 million to < \$200 million over the first six years of listing.

6.90 The evaluation and the ESC considered that the estimated cost to the PBS/RPBS of listing acalabrutinib + obinutuzumab was uncertain due to the following reasons:

- Acalabrutinib + obinutuzumab was assumed to substitute for venetoclax + obinutuzumab only. However, the evaluation considered that acalabrutinib + obinutuzumab may also substitute for chlorambucil + obinutuzumab, resulting in additional costs. The PSCR stated that substitution of chlorambucil + obinutuzumab is unlikely, given it has inferior efficacy and as such use is expected to be confined to patients intolerant of other options. The PBAC agreed with the PSCR that substitution of chlorambucil + obinutuzumab is unlikely.
- Acalabrutinib + obinutuzumab uptake may be higher than estimated in the resubmission due to longer progression-free survival for acalabrutinib + obinutuzumab compared to fixed duration venetoclax + obinutuzumab. On the other hand, the PBAC considered that some patients may prefer a fixed duration therapy, and thus overall uptake was uncertain.

6.91 The evaluation and the ESC considered that the estimated changes in use of other medicines were uncertain due to the following reasons:

- The distribution of use of second-line CLL treatments is dependent on the uptake of first-line acalabrutinib + obinutuzumab, which is uncertain.
- The approach used to estimate changes in ibrutinib and acalabrutinib script counts (based on a market share approach using PBS data) differed from the approach used to estimate the number of venetoclax + rituximab and idelalisib + rituximab scripts (assumptions). It is unclear whether the two approaches produced consistent results.
- Progression-free survival for venetoclax + obinutuzumab (used to inform the proportion of patients receiving subsequent line therapy) was estimated by applying a constant hazard ratio (derived from the unanchored MAIC) to extrapolated acalabrutinib + obinutuzumab progression-free survival data. It is unclear whether the estimated progression-free survival will reflect progression-free survival in clinical practice.

## **Financial Management – Risk Sharing Arrangements**

- 6.92 The resubmission proposed an RSA in which the cost of acalabrutinib for each patient is capped at 60 months of treatment.
- 6.93 The resubmission stated that in the financial estimates, “patients initiating treatment with acalabrutinib plus obinutuzumab in Year 1, do not receive any PBS/RPBS scripts for acalabrutinib in Year 6. The adjustment assumes no financial cost for patients on acalabrutinib from month 60 onwards despite the possibility that the patient may still be continuing therapy.” A key issue with the resubmission’s proposal is that the 60-month treatment cap would only impact the last year of the six-year financial estimates. Further, RSAs typically run for five years. Thus, the rebates to account for the duration of therapy would not be realised during the initial RSA period, despite the proposed RSA having a substantial impact on the estimated ICER.
- 6.94 The November 2021 resubmission had proposed an RSA with the cost of acalabrutinib for each patient to be capped at 48 months of treatment, which the ESC had considered to be problematic given: the lack of justification for the basis of the 48-month cap; and this was not a robust mechanism to achieve cost-effectiveness, especially given that the mean duration of treatment is likely to be much longer (paragraph 6.66, acalabrutinib, Public Summary Document, November 2021 PBAC meeting). The PBAC noted that it appeared that such an RSA would need to continue indefinitely in order to ensure that expenditure beyond the initial 48 months (4 years) of listing is capped at this treatment duration (paragraph 6.66, acalabrutinib, Public Summary Document, November 2021 PBAC meeting).
- 6.95 As detailed in paragraph 6.70, the pre-PBAC response indicated that the sponsor withdrew the RSA proposal.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend acalabrutinib, for use in combination with obinutuzumab, for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), who are considered unsuitable for treatment with fludarabine-based chemoimmunotherapy. The PBAC considered that the claim of superiority versus venetoclax + obinutuzumab was not supported and that a claim of non-inferiority would be more appropriate. As such, the PBAC considered that a cost-minimisation approach would be more appropriate, rather than the cost-utility analysis submitted. The PBAC considered that a substantial price reduction would be required for acalabrutinib + obinutuzumab to be considered acceptably cost-effective.
- 7.2 The PBAC noted the consumer comments and sponsor hearing had highlighted the high clinical need for alternative treatments, particularly BTK inhibitors, for all patients with previously untreated CLL/SLL. The PBAC considered that it would be ideal to have

a range of first-line subsidised treatment options available to patients, with treatment able to be tailored to the needs of an individual patient. Factors considered could include co-existing disease, the extent of lymph node involvement, the goals of treatment, a preference for fixed duration or continuous treatment, and the acceptability of an initial period of intravenous treatment. The PBAC noted advice from the clinician consultation that there are a lack of clinical trial data available to differentiate between regimens or determine which particular regimen would be preferable in a particular patient group/setting.

- 7.3 The PBAC noted that the requested restriction for acalabrutinib + obinutuzumab required patients to be 'inappropriate/unsuitable for fludarabine-based chemoimmunotherapy' based on the existing restrictions for venetoclax + obinutuzumab. The PBAC noted the expert advice that criteria referring to use of fludarabine are no longer relevant to clinical practice as almost all patients are 'inappropriate for fludarabine-based chemoimmunotherapy' given FCR is poorly tolerated and associated with a risk of cytopenia and secondary malignancies. The PBAC noted that FCR is no longer a preferred regimen in any patient group and is no longer commonly used in clinical practice. Thus, the PBAC advised that the existing venetoclax + obinutuzumab restriction for first-line CLL/SLL should be updated to remove this criterion. Similarly, this criterion should not be included in a restriction for acalabrutinib + obinutuzumab.
- 7.4 The PBAC noted that the restrictions for venetoclax + obinutuzumab in first-line CLL/SLL also require patients to have a CIRS score > 6 (excluding CLL-induced illness or organ damage) or a creatinine clearance < 70 mL/min, and that these criterion had also been proposed for inclusion in the acalabrutinib + obinutuzumab restriction. However, the PBAC considered that it was no longer clinically relevant to include the CIRS score in restrictions for first-line CLL/SLL therapies given it was developed to assess the ability of a patient to tolerate chemoimmunotherapy and was less relevant for targeted agents (paragraph 6.1). The PBAC considered that, rather than relying on the CIRS score and/or creatinine clearance < 70 mL/min, it would be more clinically appropriate for clinicians/patients to decide the most appropriate treatment regimen for a particular patient, which may involve consideration of a broader range of factors including biological characteristics of the disease and an individual's specific organ sensitivities (e.g. cardiac or renal risk).
- 7.5 The PBAC noted that the submission had requested listing of acalabrutinib + obinutuzumab, but not acalabrutinib monotherapy. The PBAC considered that it would be clinically appropriate to enable access to acalabrutinib monotherapy given it may be preferred by some patients due to lower toxicity compared to acalabrutinib + obinutuzumab, and given that it is an oral treatment that does not require hospital attendance for administration. The PBAC considered that, if only the combination were listed, obinutuzumab may be ceased early in clinical practice (essentially leading to the use of acalabrutinib as monotherapy). The PBAC noted that clinical evidence from the ELEVATE-TN trial was presented which supported the efficacy of

acalabrutinib monotherapy.

- 7.6 The PBAC considered the nomination of venetoclax + obinutuzumab as the main comparator was appropriate.
- 7.7 The PBAC noted that the clinical evidence included an unanchored, unmatched (naïve) indirect comparison and an unanchored MAIC of acalabrutinib + obinutuzumab (ELEVATE-TN) versus venetoclax + obinutuzumab (CLL-14). The PBAC considered that the evidence presented did not support the claim of superiority of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab as:
- there were differences in eligibility criteria between the trials (the ELEVATE-TN included patients aged  $\geq 65$  years regardless of CIRS score and creatinine clearance) and differences in patient characteristics between the trials (including median age and the proportion with a CIRS score  $>6$ ) that may have affected outcomes. Key patient characteristics data for the CLL-14 trial (including bulky disease status and Rai stage) were not available for comparison.
  - Results of the unanchored MAICs did not appear to be reliable as the MAIC did not adequately account for differences in eligibility criteria between the ELEVATE-TN and CLL-14 trials or match for potentially important prognostic variables. The PBAC acknowledged that the resubmission's updated analyses had matched on fewer variables than those presented in the July 2020 resubmission in order to increase the effective sample size, however the PBAC considered that the poor overlap between the two trials made the results of any MAIC difficult to interpret.
- 7.8 The PBAC considered that the claim of superior clinical effectiveness was not supported and that a claim of non-inferiority of acalabrutinib + obinutuzumab to venetoclax + obinutuzumab would be more appropriate. As such the PBAC considered that a cost-minimisation approach would be more informative, rather than the cost-utility analysis submitted.
- 7.9 The PBAC considered that the cost-utility analysis versus venetoclax + obinutuzumab was not informative given the model relied on data from the unanchored MAICs, which did not appear to be reliable. Further, the issues with the clinical data were magnified with an increasing benefit being modelled over time.
- 7.10 The PBAC noted that the cost per patient per course of acalabrutinib + obinutuzumab was substantially higher than venetoclax + obinutuzumab (as shown in Table 16) due to the longer treatment duration with acalabrutinib + obinutuzumab. The PBAC noted that the resubmission had proposed to partly address this through the use of an RSA with a 60 month treatment cap (in which the cost of acalabrutinib in the economic model was assumed to be nil beyond 60 months), but that this proposal was withdrawn in the pre-PBAC response due to the issues raised in paragraphs 6.70 and 6.92-6.94, with no alternative proposal presented by the sponsor. The PBAC acknowledged that the PSCR for the November 2021 resubmission had explained that the different durations of therapy between acalabrutinib and venetoclax +

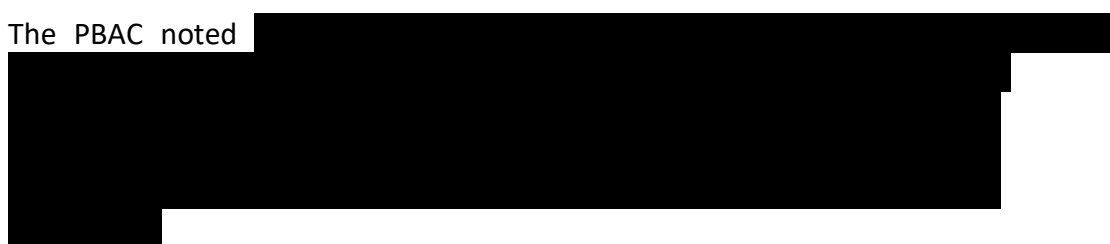
obinutuzumab would make it challenging to achieve cost-effectiveness for acalabrutinib. However, the PBAC considered that the large cost difference between acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab (nearly five times higher using the resubmission's estimated effective prices for venetoclax + obinutuzumab) was not supported by the available clinical evidence.

7.11 The PBAC agreed with the issues with the financial estimates as raised in paragraphs 6.90 and 6.91, and considered the financial estimates would need to be updated to include acalabrutinib monotherapy.

7.12 The PBAC considered a resubmission should address the following issues:

- Amend the proposed restriction to allow use of acalabrutinib as monotherapy and establish a cost-effective price for acalabrutinib monotherapy.
- Establish the equi-effective doses for treat to progression acalabrutinib + obinutuzumab compared with fixed duration venetoclax + obinutuzumab. The PBAC considered that the cost per patient per course for acalabrutinib + obinutuzumab should be no higher than for venetoclax + obinutuzumab.
- Provide revised financial estimates as outlined in paragraph 7.11.

7.13 The PBAC noted



7.14 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.15 The PBAC noted that this resubmission is eligible for an Independent Review.

7.16 Based on the advice received as part of the clinical consultation held on 1 December 2022 (paragraph 6.4), the PBAC advised that the existing PBS criteria for CLL/SLL treatments be amended as follows:

- The venetoclax + obinutuzumab restrictions for first-line CLL/SLL should be updated to remove the criterion 'inappropriate for fludarabine-based chemoimmunotherapy' and remove reference to the requirement for patients to have a CIRS score > 6 or creatinine clearance < 70 mL/min given the CIRS score was designed to predict toxicity with chemoimmunotherapy rather than targeted agents.
- The requirement for patients to be considered unsuitable for treatment or retreatment with a purine analogue should be removed from the restrictions for PBS listed drugs for CLL/SLL in the relapsed or refractory setting. The PBAC noted this would remove the notes defining this criterion (which include criteria around

factors like age and/or CIRS score and del17p).

**Outcome:**

Not recommended

## **8 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.

## **9 Sponsor's Comment**

The sponsor had no comment.