

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

1 Purpose of resubmission

- 1.1 The standard re-entry resubmission requested an Authority Required General Schedule listing of acalabrutinib 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 and venetoclax + obinutuzumab, and for patients who permanently discontinue venetoclax + obinutuzumab due to intolerance.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus chlorambucil + obinutuzumab. Listing was requested for acalabrutinib monotherapy only (previously acalabrutinib monotherapy and acalabrutinib + obinutuzumab was requested).

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

Component	Description
Population	<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"> - <u>CIRS score >6; AND</u> - <u>Renal impairment (CrCl \geq30 and <70 ml/min); AND/OR bulky disease (lymph node(s) \geq5cm); OR</u> - <u>moderate or high risk of TLS; AND</u> - <u>Unsuitable for venetoclax + obinutuzumab as unable to comply with the monitoring required for TLS prophylaxis and dose escalation requirements.</u> <p><u>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).</u></p>
Intervention	Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity.
Comparator	Oral chlorambucil for six cycles + intravenous obinutuzumab for six cycles.
Outcomes	Progression-free survival; overall response rate; time to next treatment; overall survival; safety.
Clinical claim	In patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, or who become intolerant to venetoclax + <u>obinutuzumab</u> , acalabrutinib is superior in terms of efficacy and safety compared to chlorambucil + obinutuzumab.

Source: Table 1.2, p46 of the resubmission.

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

Underlined text indicates key changes from the July 2020 submission.

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

2.2 The matters of concern from the July 2020 PBAC meeting are summarised in Table 2.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Comparators	
For the 17p deletion population, the PBAC noted that a comparison was only presented between acalabrutinib monotherapy and ibrutinib, and that no comparison was presented between acalabrutinib + obinutuzumab and ibrutinib (para 7.13, acalabrutinib, PSD, July 2020 PBAC meeting).	Listing was requested for acalabrutinib monotherapy only.
Clinical place in therapy	
The PBAC considered that the role and likely use of acalabrutinib monotherapy versus acalabrutinib + obinutuzumab was unclear (para 7.3, acalabrutinib, PSD, July 2020 PBAC meeting).	Listing was requested for acalabrutinib monotherapy only. The proposed PBS population was limited to patients with previously untreated CLL who are unsuitable for fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, or who become intolerant to venetoclax + obinutuzumab.
Clinical evidence	
The PBAC noted that acalabrutinib monotherapy demonstrated a statistically significant improvement compared to chlorambucil + obinutuzumab in terms of progression-free survival. However, the PBAC considered that the magnitude of benefit was uncertain as the data were immature (para 6.48, acalabrutinib, PSD, July 2020 PBAC meeting).	The resubmission included additional data for the ELEVATE-TN trial based on a median duration of follow-up of 46.9 months (compared to a median follow-up of 28.3 months in the July 2020 submission). Updated results were available for investigator-assessed progression-free survival, overall response rate, overall survival, and selected safety outcomes.
The PBAC considered that the efficacy and safety MAICs between both acalabrutinib monotherapy and acalabrutinib + obinutuzumab and venetoclax + obinutuzumab were highly uncertain, and that the efficacy and safety clinical claims based on the MAICs could not be supported (para 7.9, acalabrutinib, PSD, July 2020 PBAC meeting).	Venetoclax + obinutuzumab was not nominated as a comparator in the resubmission.
The PBAC considered that the efficacy and safety MAICs comparing acalabrutinib monotherapy with ibrutinib were highly uncertain. The PBAC noted the comparisons were based on the ELEVATE-TN and RESONATE trials, and, as the RESONATE trial did not include patients with 17p deletion, relied on the assumption that the outcomes in patients with 17p deletion would be the same as for patients without this deletion (para 7.14, acalabrutinib, PSD, July 2020 PBAC meeting).	Ibrutinib was not nominated as a comparator in the resubmission.
Economic analysis	

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Matter of concern	How the resubmission addresses it
The PBAC considered that the extrapolation functions should be revised to provide more plausible estimates of long-term survival and recalled that for the March 2020 submission for venetoclax for CLL in the first-line setting, a 10-year time horizon was considered to be appropriate (para 7.10, acalabrutinib, PSD, July 2020 PBAC meeting).	The model time horizon was reduced from 20 years to 15 years.
The economic model generated improvements in overall survival for patients in the acalabrutinib treatment arms which were not supported by the data from the ELEVATE-TN trial. The PBAC considered that, based on the available data, a difference in overall survival should not be modelled (para 7.10, acalabrutinib, PSD, July 2020 PBAC meeting).	Overall survival was assumed to be the same for the acalabrutinib and chlorambucil + obinutuzumab arms.
The second-line treatment options differed across the treatment arms, and there were differences in outcomes and costs for the second-line treatments which had previously been recommended on a cost-minimisation basis. The PBAC considered that the costs and benefits of venetoclax + rituximab and ibrutinib should be equal in the relapsed/refractory setting (para 7.10, acalabrutinib, PSD, July 2020 PBAC meeting).	The resubmission updated the post-progression treatment assumptions. Patients in the acalabrutinib arm were assumed to receive subsequent treatment with idelalisib + rituximab.
The mortality rates for the different lines of treatment lacked face validity (para 7.10, acalabrutinib, PSD, July 2020 PBAC meeting).	The resubmission model was based on a partitioned survival approach based on survival outcomes reported for the ELEVATE-TN trial. Post-progression treatments were used to inform costs only, with no impact applied to health outcomes.
The health state utilities used in the model from Kosmas 2015 differed considerably from the trial-based estimates. The PBAC considered that the Kosmas 2015 values re-anchored to the oral initial therapy state were more appropriate (para 7.10, acalabrutinib, PSD, July 2020 PBAC meeting).	The post-progression health state utility was based on the Kosmas 2015 estimate for progression after first-line treatment, re-anchored to the oral initial therapy state.
The length of time patients who discontinued first-line treatment remained progression free (9.2 years for acalabrutinib monotherapy patients and 10.6 years for acalabrutinib + obinutuzumab patients) was considered implausible (para 7.10, acalabrutinib, PSD, July 2020 PBAC meeting).	The resubmission model was based on a partitioned survival approach based on survival outcomes reported for the ELEVATE-TN trial, with no explicitly modelled treatment holiday.
The PBAC noted that the submission presented a cost-minimisation analysis between acalabrutinib monotherapy and ibrutinib in patients with 17p deletion. The PBAC advised that a comparison of acalabrutinib + obinutuzumab and ibrutinib would be appropriate as combination therapy is most likely to be used in patients with 17p deletion (para 7.15, acalabrutinib, PSD, July 2020 PBAC meeting).	Listing was requested for acalabrutinib monotherapy only. Ibrutinib was not nominated as a comparator in the resubmission.
Financial estimates	
The PBAC considered that the incident patient population was uncertain. The PBAC also considered that acalabrutinib +/- obinutuzumab would potentially be used outside of the proposed population in patients who are suitable for treatment with a purine analogue (para 7.12, acalabrutinib, PSD, July 2020 PBAC meeting).	Listing was requested for acalabrutinib monotherapy only (previously acalabrutinib monotherapy and acalabrutinib + obinutuzumab). The resubmission included updates to reflect the revised proposed PBS population (patients considered unsuitable for treatment with venetoclax + obinutuzumab or who permanently discontinue treatment with venetoclax + obinutuzumab due to intolerance).

Source: constructed during the evaluation using acalabrutinib, Public Summary Document, July 2020 PBAC meeting.
MAIC, matching adjusted indirect comparison; para, paragraph; PSD, Public Summary Document.

2.3 Acalabrutinib is currently listed on the PBS for relapsed or refractory CLL/SLL.

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

3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
<i>ACALABRUTINIB</i>						
ACALABRUTINIB, Treatment of patients with previously untreated CLL or SLL, 100 mg capsule, oral administration <i>acalabrutinib 100 mg capsule, 56</i>	<i>NEW</i>	1	56	5	\$8,218.96 published price \$ effective price	Calquence
				Max.qty (packs) multiplier = 2 Repeat increases: nil		
Restriction Summary [new] / Treatment of Concept: [new]						
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via <i>Online PBS Authorities</i>						
Administrative advice: <i>No increase in the maximum number of repeats may be authorised.</i>						
Administrative advice: <i>Special Pricing Arrangements apply.</i>						
Administrative advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>						
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)						
Indication: Patients with previously untreated CLL/SLL <i>Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)</i>						
Treatment Phase: Initial						
Clinical criteria:						
The condition must be previously untreated, OR Patient who commenced venetoclax in combination with obinutuzumab but experienced intolerance/adverse event requiring permanent discontinuation of treatment. OR <i>Patient must have received PBS-subsidised treatment with venetoclax in combination with obinutuzumab for this condition but experienced intolerance/adverse event necessitating permanent treatment withdrawal,</i>						
AND						
Clinical criteria:						
Patient must be considered unsuitable for fludarabine based chemoimmunotherapy, <i>Patient must be inappropriate for fludarabine based chemo-immunotherapy,</i>						
AND						
Clinical criteria:						
<i>Patient must have a creatinine clearance 30 mL/min or greater,</i>						
AND						
Clinical criteria:						
<i>Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage)</i>						

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	AND
	Clinical criteria:
	Patient must have renal impairment defined as a creatinine clearance of ≥ 30 mL/min but < 70 mL/min, Patient must have a creatinine clearance less than 70 mL/min. AND/OR Patient must have has bulky disease (lymph nodes ≥ 5 cm), OR Patient must have has moderate or high risk of developing tumour lysis syndrome (TLS),
	AND
	Clinical criteria:
	Patient is unsuitable for venetoclax in combination with obinutuzumab as unable to comply with monitoring requirements for tumour lysis syndrome (TLS) prophylaxis and venetoclax dose escalation schedule. Patient must be unsuitable for venetoclax in combination with obinutuzumab for the treatment of CLL/SLL as unable to comply with the monitoring requirements for tumour lysis syndrome (TLS) prophylaxis, OR Patient must be unsuitable for venetoclax in combination with obinutuzumab for the treatment of CLL/SLL as unable to comply with the venetoclax dose escalation schedule,
	Clinical criteria:
	The treatment must be as monotherapy for this condition
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined <input checked="" type="checkbox"/> Authority Required via Online PBS Authorities
	Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Indication: Patients with previously untreated CLL/SLL Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Continuing
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be as monotherapy for this condition

- 3.2 The resubmission proposed a special pricing arrangement, with an effective price of ██████% of the proposed published price. The proposed price was lower than the price proposed in the July 2020 submission (effective DPMQ: \$ ██████; published DPMQ: \$ ██████). The proposed effective price was the same as the effective price for acalabrutinib under the current relapsed/refractory CLL/SLL PBS listing.
- 3.3 The proposed restriction was narrower than the TGA indication, which does not restrict treatment on the basis of CIRS score, renal function, tumour lysis syndrome risk, or intolerance/unsuitability for treatments.

- 3.4 The proposed clinical criteria were narrower than the eligibility criteria for the ELEVATE-TN trial, which recruited patients with previously untreated CLL aged ≥ 65 years and patients aged < 65 years meeting additional criteria (creatinine clearance of 30-69 mL/min or a CIRS score > 6). The proposed restriction did not include a performance status requirement, whereas the ELEVATE-TN trial inclusion criteria specified an ECOG performance score of ≤ 2 .
- 3.5 The proposed clinical criteria were difficult to interpret and required rewording to remove ambiguity and to meet the electronic requirements of listing.
- 3.6 The Pre-Sub-Committee Response (PSCR) articulated that the proposed PBS population could be split into two patient groups:
- **Group 1:** Patients unsuitable for VTX+OBIN with one or more clinical characteristics:
 - renal impairment (creatinine clearance less than 70 mL/min) OR
 - bulky disease (lymph nodes ≥ 5 cm)
 - AND
 - are unable to comply with the venetoclax dose escalation schedule OR
 - are unable to comply with monitoring requirements for tumour lysis syndrome (TLS) prophylaxis.
 - **Group 2:** Patients who initiated VTX+OBIN but experienced intolerance/adverse event requiring permanent discontinuation of treatment.
- 3.7 The PSCR accepted the Secretariat's proposed changes to the restriction, but considered that patients in Group 2 should not be required to meet all other criteria associated with the proposed initial phase listing, as they must have previously qualified for treatment with venetoclax + obinutuzumab. Given this, the Secretariat advised that a separate initial phase listing would likely be required for these patients. It was unclear to the Secretariat if any clinical criteria would be applied to this listing beyond limiting to monotherapy and requiring that a "Patient must have received PBS-subsidised treatment with venetoclax in combination with obinutuzumab for this condition but experienced intolerance/adverse event necessitating permanent treatment withdrawal". The PBAC considered that additional clarification may be required to indicate that these patients must have discontinued treatment prior to disease progression or completing a treatment course. The pre-PBAC response provided further expert commentary on the restriction and proposed further minor amendments. The PBAC specifically raised that it may not be reasonable to require that patients have both a CIRS > 6 **and** CrCL ≤ 70 mL/min, given this is more restrictive than first-line listings for obinutuzumab + chlorambucil and venetoclax + obinutuzumab. Also, given bulky disease is a risk factor for TLS, it does not need to be separately specified in the criteria.
- 3.8 The PSCR also claimed that unsuitability for venetoclax + obinutuzumab is clearly understood in clinical practice and is defined in current guidelines (National Comprehensive Cancer Network (NCCN), 2021, eviQ, 2018). It was unclear which parts

of the respective guidelines the sponsor was referring to. The PSCR listed patients with cognitive impairment, patients with no enabling carer, and patients living in regional or remote locations who are unable to access home or hospital-based care for IV infusions as examples of patients who are unable to comply with the venetoclax dose escalation schedule. The PSCR listed patients living in regional/remote locations who cannot access hospital-based care with rapid turn-around laboratory results, elderly or frail patients with no access to enabling carer support/transport services, and patients who need home-based care, as examples of patients unable to comply with monitoring requirements for tumour lysis syndrome prophylaxis.

- 3.9 The ESC noted that the PSCR had not proposed any specific additions to the listing criteria or Prescriber Instructions to define (un)suitability for venetoclax + obinutuzumab. The ESC also noted that most definitions proposed in the paragraph above were highly subjective, and it was unclear whether prescribing choices would be influenced by the availability of acalabrutinib in the first-line setting.
- 3.10 A large proportion of the previously untreated CLL/SLL population are likely to meet the included tumour lysis syndrome risk requirements. Baseline characteristics for the CLL-14 trial assessing venetoclax + obinutuzumab versus chlorambucil + obinutuzumab in previously untreated CLL suggest that 13% had a low risk of tumour lysis syndrome risk, 66% had an intermediate risk, and 21% had a high risk.
- 3.11 The proposed restriction did not limit use of acalabrutinib to monotherapy. There may be potential for use of acalabrutinib in combination with obinutuzumab given positive results for treatment with acalabrutinib + obinutuzumab in the ELEVATE-TN trial. The ESC considered that the restriction should explicitly limit use to monotherapy, as this was the clinical position proposed by the resubmission.
- 3.12 The resubmission noted that the sponsor may initiate a patient access program if PBAC recommended the requested listing “for a finite period while PBS listing arrangements are finalised”. A proposed grandfathering restriction was included for this purpose, but the sponsor had not provided any financial estimates.

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

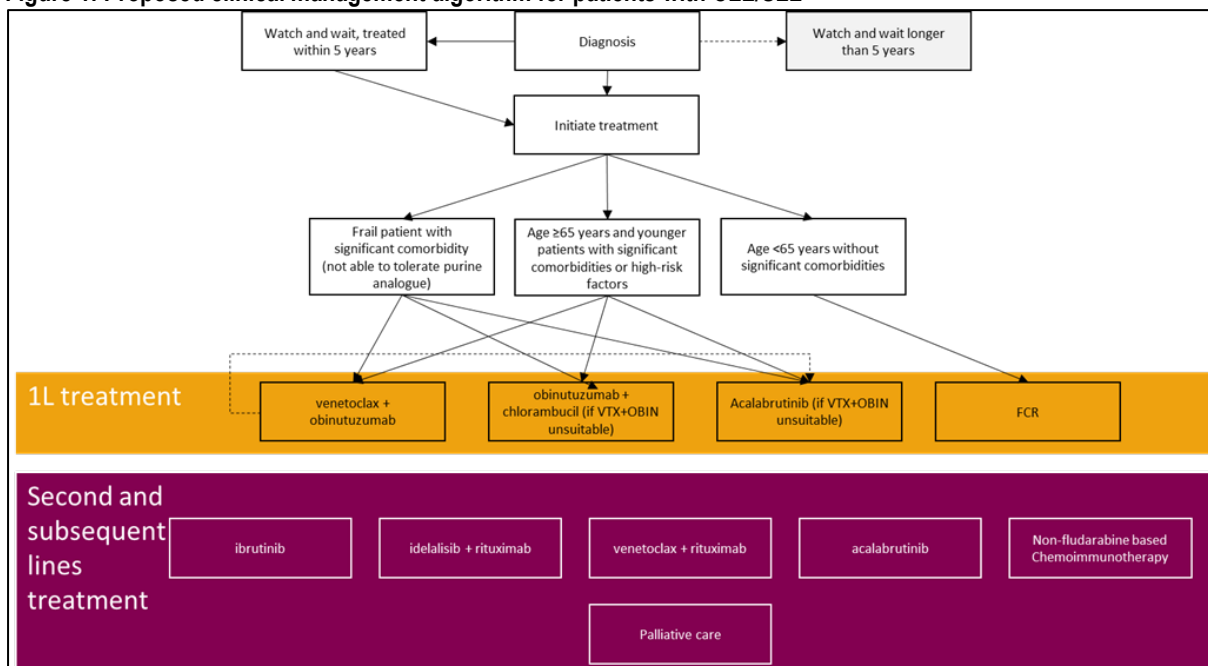
4 Population and disease

- 4.1 CLL is characterised by the progressive accumulation of functionally incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, spleen, and liver. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating, and unintentional weight loss.
- 4.2 CLL is more common in men than women (62% versus 38%), with a mean age at diagnosis in Australia of 70.6 years (males 69.9 years, females 71.8 years). The five-year relative survival rate in Australia in 2013-2017 was 84.9% (AIHW, 2021). 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.

- 4.3 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 several factors, including age, fitness, comorbidities, and the presence of prognostic genetic mutations.
- 4.5 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.
- 4.6 Figure 1 presents the resubmission’s proposed clinical management algorithm.

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



Source: Figure 1.4, p57 of the resubmission.

FCR, fludarabine + cyclophosphamide + rituximab; OBIN, obinutuzumab; VTX, venetoclax.

- 4.7 The algorithm positioned acalabrutinib monotherapy as a first-line option for 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; who are considered unsuitable for treatment with venetoclax + obinutuzumab. The resubmission also requested listing of acalabrutinib for patients who permanently discontinue treatment with venetoclax + obinutuzumab due to intolerance. These patients were not explicitly included in the treatment algorithm.

- 4.8 The resubmission argued that, based on expert opinion, there is a clinical need for additional therapies among previously untreated patients who are unsuitable for treatment with fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, due to the lower effectiveness of chlorambucil + obinutuzumab. The ESC recognised there was a clinical rationale for the narrower listing, but noted that the clinical need identified in the resubmission could also be addressed with a broader listing extended to the population who are unsuitable for fludarabine based chemotherapy. The resubmission claimed that patients who discontinue treatment with venetoclax + obinutuzumab due to intolerance have limited treatment options, as they do not meet eligibility requirements for PBS-listed relapsed/refractory treatments.
- 4.9 The PSCR explained that achieving cost-effectiveness for a broader listing would be challenging as acalabrutinib monotherapy is used until disease progression or unacceptable toxicity, potentially for several years, compared with venetoclax + obinutuzumab, which has a fixed duration of 48 weeks. Hence, the sponsor had identified a narrower population in which there was a clinical need for alternative treatment options.
- 4.10 The resubmission assumed that approximately 16% of patients who are eligible for treatment with venetoclax + obinutuzumab would develop intolerance to venetoclax + obinutuzumab requiring permanent discontinuation, and that approximately 14% of patients are unsuitable for treatment with venetoclax + obinutuzumab. The ESC noted that the 16% appeared to be based on the proportion of patients who discontinued at least one treatment component of venetoclax + obinutuzumab due to adverse events in the CLL-14 trial (Fischer et al., 2019) (see also Table 16: Key inputs for financial estimates). Overall, the population targeted in the resubmission was unclear due to a lack of definition for unsuitability for venetoclax + obinutuzumab treatment. Although the PSCR provided examples of patients who might be unsuitable, the ESC again noted that most were highly subjective, and thus it was unclear whether prescribing choices would be influenced by the availability of acalabrutinib in the first-line setting.
- 4.11 The July 2020 submission requested listing for acalabrutinib monotherapy and acalabrutinib + obinutuzumab, whereas the current resubmission requested listing for acalabrutinib monotherapy only. The rationale for limiting treatment to acalabrutinib monotherapy in the resubmission was unclear. This did not appear to be addressed in the PSCR, although the ESC considered that, in the context of the proposed population, limiting to use as monotherapy may be appropriate as these patients may be less fit for treatment with the combination regimen. Acalabrutinib and acalabrutinib + obinutuzumab are both listed as preferred treatments among patients

with previously untreated CLL/SLL in the current NCCN treatment guidelines (Version 3.2021, 2021).

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

5 Comparator

- 5.1 The resubmission nominated chlorambucil + obinutuzumab as the main comparator. The resubmission claimed that chlorambucil + obinutuzumab is the treatment most likely to be replaced among patients who are considered unsuitable for treatment with fludarabine-based chemotherapy and venetoclax + obinutuzumab, or who develop intolerance necessitating permanent withdrawal of venetoclax + obinutuzumab.
- 5.2 The PBAC previously considered that chlorambucil + obinutuzumab was an appropriate comparator for patients with previously untreated CLL who are unsuitable for treatment with a purine analogue. However, the evaluation suggested it was unclear whether chlorambucil + obinutuzumab was the appropriate main comparator for the PBS population targeted in the resubmission, given the following:
- Choice of treatment among patients who permanently discontinue venetoclax + obinutuzumab treatment due to intolerance is likely to depend on whether discontinuation was due to one or both components of the treatment, which component required discontinuation, and the timing of discontinuation in relation to the 12-month treatment course. Patients who discontinue treatment with venetoclax + obinutuzumab due to intolerance of venetoclax would be ineligible for treatment with chlorambucil + obinutuzumab as the obinutuzumab PBS restriction for use in combination with chlorambucil requires patients to be previously untreated. The PSCR argued that this means there are no active treatments available for these patients, and given the resubmission assumed an active comparator for all patients, the efficacy and cost-effectiveness estimates are potentially biased against acalabrutinib. The ESC considered that this would be a very small patient population and would not impact the efficacy or cost-effectiveness estimates to a significant degree.
 - Based on the proposed restriction, patients are considered unsuitable for venetoclax + obinutuzumab if they are at moderate or high risk of tumour lysis syndrome and are unable to comply with monitoring requirements for tumour lysis syndrome prophylaxis and venetoclax dose escalation schedule. It is unclear how the restriction criteria would be interpreted in clinical practice. Patients/clinicians may also elect treatment with acalabrutinib due to preference for an oral therapy and/or a therapy that does not require hospital attendance. In this case, venetoclax + obinutuzumab may be an appropriate comparator. The PSCR argued that it is also plausible that patients may prefer a significantly shorter treatment regimen, even with the requirement of hospitalisation and increased monitoring, unless they were considered clinically unsuitable for treatment with

venetoclax + obinutuzumab. It claimed this was supported by research with CLL patients, which demonstrated a weak preference for oral therapy which was outweighed by efficacy and safety considerations (Mansfield et al., 2017).

- 5.3 Ibrutinib monotherapy was nominated as a comparator in the July 2020 acalabrutinib submission for patients with 17p deletion. The current resubmission argued that ibrutinib was no longer a relevant comparator given that a PBS listing has not eventuated following the positive recommendation at the November 2019 PBAC meeting.

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 discussed the natural history of the disease and emphasised the challenges of using infusion-based chemotherapy for treating patients living in regional and rural areas. The clinician also described how older patients often have declining renal function making them less suitable for infusion-based chemotherapy treatments. The clinician further noted that BTKi treatments like acalabrutinib have superior outcomes for CLL compared with chlorambucil + obinutuzumab in the first-line setting. The risks of TLS associated with venetoclax + obinutuzumab therapy were also described, with discussion of the increased hospital resources used to monitor and manage this risk. The clinician particularly commented on the inequity of available treatment choices for patients not living in close proximity to major tertiary treatment centres, and explained that patients may choose inferior treatments because they are unable to travel to the hospital for the frequency and duration required, due to either their own personal circumstances, or the impact it may have on their family members. The sponsor hearing also highlighted the individual story of a patient with CLL who, after an initial long period managed via a “watch-and-wait” approach, was treated with acalabrutinib via a clinical trial. This patient experienced a side effect of increased fatigue for some weeks, but then regained energy, quality of life, and improved mental clarity. The clinician highlighted that this was a common experience for patients using acalabrutinib, and stated that patients would benefit from knowing their disease was being controlled.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. The comments noted that there are currently no BTKis that are PBS-subsided for previously untreated CLL/SLL, and that acalabrutinib's oral form may assist regional/rural patients to access therapy, as it would not require admission to a day hospital unit. Comments were received from the Centre for Community-Driven

Research, Rare Cancers Australia, and the Leukaemia Foundation, in support of the PBS listing. The Leukaemia Foundation highlighted the experiences of three patients who have taken acalabrutinib for previously untreated CLL/SLL where they variously experienced improved quality of life, energy and a more positive outlook. Some patients experienced increased fatigue, but fewer side-effects overall than chemotherapy, others highlighted the convenience of the oral form. Clinical outcomes such as partial remission induction and improved blood counts were also noted. The CCDR presented survey data (n=70), mostly collected in 2020, on various aspects of the lived experience of CLL/SLL, although no specific discussion of acalabrutinib treatment itself.

Clinical trials

- 6.3 The resubmission was based on one head-to-head randomised trial comparing acalabrutinib and acalabrutinib + obinutuzumab to chlorambucil + obinutuzumab (ELEVATE-TN trial). The ELEVATE-TN trial was previously considered by the PBAC as part of the July 2020 submission.
- 6.4 Details of the trial reports presented in the resubmission are provided in the table below.

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.	PowerPoint slides, Attachment 8 of the resubmission, 7 January 2021.
	Sharman J, Banerji V, Fogliatto L, Herishanu Y, Munir T. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Cib) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL).	<i>Blood</i> 2019; 134 (Supplement 1): 31.
	Sharman J, Egyed M, Jurczak W, Sharbnik A, Pagal J et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukaemia: ELEVATE-TN four-year follow up.	<i>Journal of Clinical Oncology</i> 2021; 39 (15_suppl): 7509-7509.
	Sharman J, Egyed M, Jurczak W, Sharbnik A, Pagal J et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukaemia: ELEVATE-TN four-year follow up.	ASCO Meeting Library 2021 (poster).
	Sharman J, Egyed M, Jurczak W, Sharbnik A, Pagal J 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.	<i>The Lancet</i> 2020; 395 (10232): 1278-1291.
	Martens U, Sharman J, Banerji V, Fogliatto L, Herishanu Y et al. ELEVATE TN phase 3 study of acalabrutinib plus obinutuzumab or acalabrutinib monotherapy vs chlorambucil plus obinutuzumab (CLBO) in subjects with previously untreated chronic lymphocytic leukemia (CLL).	<i>Oncology Research and Treatment</i> 2020; 43 (Supplement 1): 127.
	Munir T, Sharman J, Banerji V, Fogliatto L, Herishanu Y et al. ELEVATE-TN: a phase 3, multicentre, open-label study of acalabrutinib (Ab) combined with obinutuzumab (O) or Ab alone versus O plus chlorambucil (Cib) in patients (pts) with treatment-naive chronic lymphocytic leukaemia (TN-CLL).	<i>British Journal of Haematology</i> 2020; 189 (Supplement 1): 26-28.
	Walker P, Sharman JP, Jurczak W, Munir T, Banerji V et al. Patient-reported outcomes from the phase 3, randomized study of acalabrutinib with or without obinutuzumab versus chlorambucil plus obinutuzumab for treatment-naive chronic lymphocytic leukemia (ELEVATE-TN). ^a	<i>Value in Health</i> 2021; 24 (Supplement 1): S3-S4.

Source: Table 2.5, p71 of the resubmission.

^a Identified during the evaluation.

6.5 The key features of the ELEVATE-TN trial are summarised in the table below.

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
Acalabrutinib + obinutuzumab vs. acalabrutinib monotherapy vs. chlorambucil + obinutuzumab						
ELEVATE-TN	535	Phase 3, randomised, open-label trial. Median duration of follow-up: - 28.3 months for the February 2019 interim analysis - 46.9 months for the September 2020 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 ^a - Adverse events - Health-related quality of life (FACIT-Fatigue, EORTC QLQ-C30, EQ-5D-3L) ^a	- Progression-free survival - Overall survival - Time to next treatment ^a - Adverse events - EQ-5D-3L ^a

Source: Table S1, pp2-4 and pp42-46 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; QLQ-C30, quality of life questionnaire Core 30.

^a Results based on the February 2019 interim analysis (no additional results available for the September 2020 data cut)

- 6.6 The ELEVATE-TN trial had an unclear risk of bias. The trial was an open-label trial, and investigators, patients, and study personnel were not blinded to treatment allocation, which may have influenced the treatment of patients in the trial. The trial included assessments by study investigators as well as blinded assessments by an independent review committee. Assessments made by the blinded independent review committee are at lower risk of assessment bias compared to assessments made by study investigators. Overall survival results were impacted by patient crossover from the chlorambucil + obinutuzumab arm to receive treatment with acalabrutinib monotherapy.
- 6.7 The ELEVATE-TN trial included three treatment arms: acalabrutinib monotherapy, acalabrutinib + obinutuzumab, and chlorambucil + obinutuzumab. Treatment with acalabrutinib was ongoing until disease progression or patients experienced unacceptable toxicity. Treatment with obinutuzumab and chlorambucil was based on a fixed treatment duration of six cycles (approximately six months).
- 6.8 Patients in the chlorambucil + obinutuzumab arm 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 September 2020 data cut, 39% of patients in the chlorambucil + obinutuzumab arm had received crossover treatment with acalabrutinib following disease progression.
- 6.9 At the September 2020 data cut, treatment with acalabrutinib was ongoing in 134 (74.9%) patients in the acalabrutinib + obinutuzumab arm and 124 (69.3%) patients in the acalabrutinib arm. Eight patients (4.5%) in the acalabrutinib + obinutuzumab arm, 21 patients (11.7%) in the acalabrutinib arm, and 15 patients (8.5%) in the chlorambucil + obinutuzumab arm had received at least one subsequent anticancer

treatment at the September 2020 data cut (excluding chlorambucil + obinutuzumab patients treated with acalabrutinib). Nine patients (5.0%) in the acalabrutinib monotherapy arm had received subsequent treatment with venetoclax.

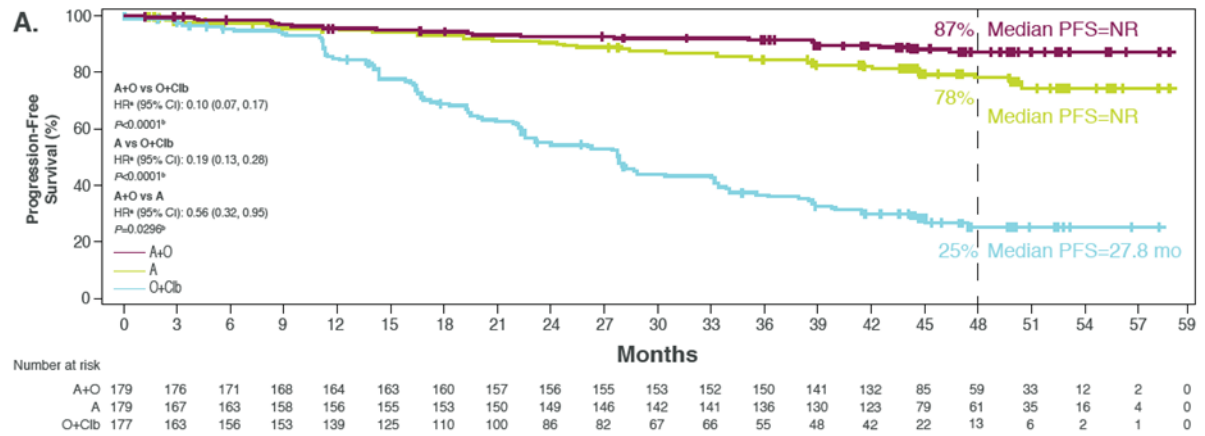
- 6.10 The applicability of the results to the proposed PBS population was unclear to the evaluation, due to differences between the ELEVATE-TN trial inclusion criteria (patients aged ≥ 65 years and patients aged 18 to 65 years with a creatinine clearance of 30 to 69 mL/min or CIRS score >6), and the proposed PBS population, which is restricted to patients considered unsuitable for treatment with fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, and patients who permanently discontinue treatment with venetoclax + obinutuzumab due to intolerance. The PSCR argued that there was no reason to suggest that patients with characteristics that make them unsuitable for treatment with venetoclax + obinutuzumab would not have been included in the ELEVATE-TN trial. It also stated that since these patients cannot be identified with the trial inclusion criteria, no specific subgroup analysis could be presented. However, it did note that the resubmission also included an analysis showing that key clinical variables such as creatinine clearance and bulky disease were not treatment effect modifiers. Finally, the PSCR argued that the trial inclusion criteria and study populations of the CLL-14 study¹ and ELEVATE-TN were very similar, and hence patients who qualified for venetoclax + obinutuzumab treatment but needed to discontinue due to toxicity/adverse events could also have been suitable for inclusion in the ELEVATE-TN trial. The ESC considered that poor renal function would be an important reason why patients might be unsuitable for fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, and hence it considered that ELEVATE-TN results would be reasonably applicable to the proposed PBS population.

Comparative effectiveness

- 6.11 The July 2020 submission was based on the results of an interim analysis in February 2019, at a median follow-up of 28.3 months. The resubmission provided additional data from a September 2020 data cut, corresponding to a median duration of follow-up of 46.9 months. Updated results were only available for investigator-assessed progression-free survival, overall response rate, overall survival, and selected safety outcomes.
- 6.12 Figure 2 presents the Kaplan-Meier plot of investigator-assessed progression free survival for the ELEVATE-TN trial based on a median duration of follow-up of 46.9 months.

¹ Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia.

Figure 2: Kaplan-Meier plot of investigator-assessed progression-free survival for the ELEVATE-TN trial at a median follow-up of 46.9 months



Source: Figure 2.3, p90 of the resubmission (Figure 1A of Sharman et al. 2021).

A, acalabrutinib; Cb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

6.13 Table 5 summarises the results for independent review committee and investigator-assessed progression-free survival for the ELEVATE-TN trial at the interim analysis and at the September 2020 data cut.

Table 5: Progression-free survival results for the ELEVATE-TN trial at the February 2019 interim analysis and for the September 2020 data cut

	Feb 2019 data cut			Sep 2020 data cut		
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)
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)	47.0 (1.7-59.2)	46.9 (0.1-59.4)	46.2 (0.0-58.4)
Independent review committee-assessed						
Earliest event total, n (%)	14 (7.8)	26 (14.5)	93 (52.5)	NR	NR	NR
- Progression, n (%)	9 (5.0)	20 (11.2)	82 (46.3)	NR	NR	NR
- Death, n (%)	5 (2.8)	6 (3.4)	11 (6.2)	NR	NR	NR
Median PFS, months (95% CI)	Not reached (NE)	Not reached (34.2, NE)	22.6 (20.2, 27.6)	NR	NR	NR
Stratified HR vs CHL + OBI (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-	NR	NR	-
KM estimate of PFS						
- 12 months, % (95% CI)	95.9 (91.7, 98.0)	92.9 (87.8, 95.9)	84.6 (78.0, 89.3)	NR	NR	NR
- 24 months, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)	NR	NR	NR
- 36 months, % (95% CI)	89.6 (82.0, 94.1)	63.9 (29.4, 84.9)	31.3 (21.8, 41.3)	NR	NR	NR
Investigator-assessed						
Earliest event total, n (%)	15 (8.4)	19 (10.6)	86 (48.6)	21 (11.7)	36 (20.1)	115 (65.0)
- Progression, n (%)	9 (5.0)	12 (6.7)	75 (42.4)	12 (6.7)	22 (12.3)	103 (58.2)
- Death, n (%)	6 (3.4)	7 (3.9)	11 (6.2)	9 (5.0)	14 (7.8)	12 (6.8)
Median PFS, months (95% CI)	Not reached (NE)	Not reached (NE)	27.8 (22.6, 28.8)	Not reached (NE)	Not reached (NE)	27.8 (22.6, 33.2)
Stratified HR vs CHL + OBI (95% CI)	0.12 (0.07, 0.21)	0.16 (0.10, 0.27)	-	0.10 (0.07, 0.17)	0.19 (0.13, 0.28)	-
KM estimate of PFS						
- 12 months, % (95% CI)	95.4 (91.1, 97.7)	94.7 (90.1, 97.2)	85.5 (79.1, 90.0)	95.4 (91.1, 97.7)	94.7 (90.1, 97.2)	84.8 (78.4, 89.5)
- 24 months, % (95% CI)	91.9 (86.7, 95.1)	90.4 (84.9, 94.0)	54.7 (46.7, 62.0)	92.5 (87.4, 95.6)	90.5 (84.9, 94.0)	55.0 (47.0, 62.3)
- 36 months, % (95% CI)	90.9 (85.3, 94.5)	87.6 (81.0, 92.1)	36.9 (26.6, 47.1)	91.3 (86.0, 94.7)	84.3 (77.8, 89.1)	36.7 (29.2, 44.2)
- 48 months, % (95% CI)	-	-	-	87.0 (80.6, 91.4)	77.9 (70.2, 83.9)	25.1 (17.9, 32.9)
- 54 months, % (95% CI)	-	-	-	87.0 (80.6, 91.4)	74.3 (65.1, 81.5)	25.1 (17.9, 32.9)

Source: Table 2.15, p65 of the resubmission; Table 14.2.5.1, pp1-2 of Attachment 12 of the resubmission; Table 14, pp97-98; Table 22, p121 of the ELEVATE-TN interim clinical study report.

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.

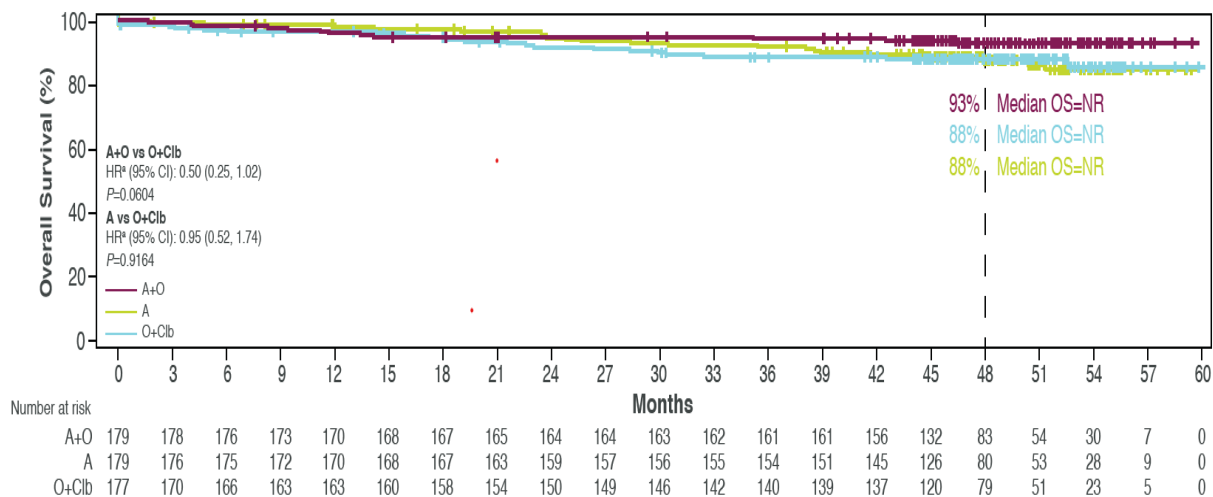
Bold indicates statistically significant results.

6.14 At a median duration of follow-up of 46.9 months, 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 (median progression-free survival not reached in either acalabrutinib arm versus 27.8 months for chlorambucil + obinutuzumab; HR = 0.10 [95% CI: 0.07, 0.17] for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab; HR = 0.19 [95% CI: 0.13, 0.28] for acalabrutinib monotherapy versus

chlorambucil + obinutuzumab). A *post hoc* analysis comparing progression-free survival between the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms was suggestive of a statistically significant difference in favour of acalabrutinib + obinutuzumab compared to acalabrutinib monotherapy (Sharman et al., 2021).

- 6.15 The PBAC previously noted that, due to the immaturity of the data, the magnitude of the effectiveness benefit was uncertain (paragraph 6.48, acalabrutinib, Public Summary Document (PSD), July 2020 PBAC meeting). The ESC noted that updated data for the ELEVATE-TN trial presented in the resubmission (median duration of follow-up 46.9 months) indicated that the progression-free survival benefit for acalabrutinib monotherapy versus chlorambucil + obinutuzumab observed at the interim analysis was maintained, however, median progression-free survival was not reached in the acalabrutinib monotherapy or acalabrutinib + obinutuzumab arms.
- 6.16 Treatment with acalabrutinib + obinutuzumab was associated with a numerical improvement in progression-free survival at 54 months compared to acalabrutinib monotherapy (87.0% versus 74.3%). A *post hoc* analysis published by Sharman et al. (2021) was suggestive of a statistically significant difference in favour of acalabrutinib + obinutuzumab (HR = 0.56 [95% CI: 0.32, 0.95]).
- 6.17 Figure 3 presents the Kaplan-Meier plot of overall survival for the ELEVATE-TN trial at a median duration of follow-up of 46.9 months.

Figure 3: Kaplan-Meier plot of overall survival for the ELEVATE-TN trial at a median duration of follow-up of 46.9 months



Source: Attachment 10 of the resubmission (Figure 4 of Sharman et al., 2021).

A, acalabrutinib; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; OS, overall survival.

^a Hazard ratio was based on stratified Cox-Proportional-Hazards model (stratified by 17p deletion status)

- 6.18 Table 6 presents the results for overall survival for the ELEVATE-TN trial at the September 2020 data cut (median follow-up of 46.9 months).

Table 6: Overall survival results for the ELEVATE-TN trial at the September 2020 data cut (median duration of follow-up of 46.9 months)

Cohort	Sep 2020 data cut		
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)
Median duration of follow-up, months (range)	47.0 (1.7-59.2)	46.9 (0.1-59.4)	46.2 (0.0-58.4)
Death, n (%)	12 (6.7)	22 (12.3)	21 (11.9)
Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	Not reached (NE)
Stratified HR vs CHL + OBI (95% CI)	0.50 (0.25, 1.02)	0.95 (0.52, 1.74)	-
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)
- 24 months, % (95% CI)	94.9 (90.5, 97.3)	94.8 (90.2, 97.2)	91.7 (86.4, 95.0)
- 36 months, % (95% CI)	94.3 (89.7, 96.9)	91.8 (86.5, 95.1)	88.6 (82.7, 92.6)
- 48 months, % (95% CI)	92.9 (87.7, 95.9)	87.6 (81.3, 91.9)	88.0 (82.0, 92.1)
- 54 months, % (95% CI)	92.9 (87.7, 95.9)	84.5 (76.6, 89.9)	85.5 (77.2, 91.0)

Source: Table 2.20, p98 of the resubmission; Table 14.2.4, pp1-2 of Attachment 11 of the resubmission.

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

- 6.19 At a median duration of follow-up of 46.9 months, median overall survival was not reached in any treatment arm. There was no statistically significant difference for acalabrutinib + obinutuzumab, or acalabrutinib monotherapy compared to chlorambucil + obinutuzumab. However, the overall survival results remained immature.
- 6.20 The proportion of patients alive in the acalabrutinib + obinutuzumab arm at 54 months (92.9%; 95% CI: 87.7, 95.9) was numerically higher than the acalabrutinib monotherapy (84.5%; 95% CI: 76.6, 89.9) and chlorambucil + obinutuzumab arms (85.5%; 95% CI: 77.2, 91.0). Results for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab appeared to be approaching statistical significance.
- 6.21 Table 7 presents the results for independent review committee- and investigator-assessed overall response for the ELEVATE-TN trial at the interim analysis and for the September 2020 data cut.

Table 7: Overall response results for the ELEVATE-TN trial at the February 2019 interim analysis and for the September 2020 data cut

Cohort	Feb 2019 data cut			Sep 2020 data cut		
	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)
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)	47.0 (1.7-59.2)	46.9 (0.1-59.4)	46.2 (0.0-58.4)
Independent review committee-assessed						
ORR (CR + CRi + nPR + PR), n (%)	168 (93.9)	153 (85.5)	139 (78.5)	NR	NR	NR
Difference versus CHL + OBI (95% CI)	15.3 (8.3, 22.3)	6.9 (-1.0, 14.9)	-	NR	NR	-
Investigator-assessed						
ORR (CR + CRi + nPR + PR), n (%)	172 (96.1)	160 (89.4)	146 (82.5)	172 (96.1)	161 (89.9)	146 (82.5)
Difference versus CHL + OBI (95% CI)	13.6 (7.3, 19.9)	6.9 (-0.3, 14.1)	-	13.6 (NR)	7.5 (0.3, 14.6)	-

Source: Table 2.17, pp94-95; Table 2.18, p95 of the resubmission; Table 18, p110 of the ELEVATE-TN interim clinical study report; p10 of Attachment 8 of the resubmission; Sharman et al. (2021), Attachment 10 of the submission.

ACAL, acalabrutinib; CHL, chlorambucil; CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; OBI, obinutuzumab; overall response rate; ORR, overall response rate; PR, partial response.

Bold indicates statistically significant results.

- 6.22 Based on the independent review committee-assessed outcomes at the February 2019 interim analysis, the overall response rate was higher in the acalabrutinib + obinutuzumab (93.9%) and acalabrutinib monotherapy (85.5%) arms compared to the chlorambucil + obinutuzumab arm (78.5%). The difference was statistically significant for the acalabrutinib + obinutuzumab comparison (difference: 15.3% [95% CI: 8.3, 22.3]), but not the acalabrutinib monotherapy comparison (difference: 6.9% [95% CI: -1.0, 14.9]).
- 6.23 Based on investigator-assessed outcomes for the September 2020 data cut (median follow-up of 46.9 months), the overall response rate was higher in the acalabrutinib + obinutuzumab (96.1%) and acalabrutinib monotherapy arms (89.9%), compared to the chlorambucil + obinutuzumab arm (82.5%). The difference was statistically significant for the comparison of acalabrutinib monotherapy versus chlorambucil + obinutuzumab (difference: 7.5% [95% CI: 0.3, 14.6]). Results of statistical testing for the difference between the acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab arms were not available.
- 6.24 Table 8 presents the results for time to next anti-CLL treatment for the ELEVATE-TN trial at the February 2019 interim analysis. No new data for time to next anti-CLL treatment were presented in the resubmission.

Table 8: Time to next treatment results for the ELEVATE-TN trial at the February 2019 interim analysis

Cohort	ACAL + OBI (N=179)	ACAL (N=179)	CHL + OBI (N=177)
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)
Independent review committee-assessed			
Total events, n (%)	13 (7.3)	21 (11.7)	70 (39.5)
- Death, n (%)	8 (4.5)	10 (5.6)	15 (8.5)
- Crossover treatment, n (%)	0	0	45 (25.4)
- Subsequent anti-cancer therapy, n (%)	5 (2.8)	11 (6.1)	10 (5.6)
Median TTNT, months (95% CI)	Not reached (NE)	Not reached (NE)	Not reached (28.9, NE)
Stratified HR vs CHL + OBI (95% CI)	0.14 (0.08, 0.26)	0.24 (0.15, 0.40)	-
KM estimate of TTNT			
- 6 months, % (95% CI)	97.8 (94.2, 99.2)	96.6 (92.6, 98.5)	95.3 (90.9, 97.6)
- 12 months, % (95% CI)	94.9 (90.5, 97.3)	94.3 (89.7, 96.9)	92.9 (87.9, 95.9)
- 18 months, % (95% CI)	93.2 (88.4, 96.1)	92.6 (87.5, 95.6)	78.5 (71.5, 84.0)
- 24 months, % (95% CI)	93.2 (88.4, 96.1)	90.2 (84.7, 93.8)	67.0 (59.2, 73.6)
- 30 months, % (95% CI)	93.2 (88.4, 96.1)	87.9 (81.8, 92.1)	55.5 (46.5, 63.5)
- 36 months, % (95% CI)	90.0 (80.0, 95.2)	86.3 (79.2, 91.1)	50.2 (40.3, 59.3)

Source: Table 2.19, p96 of the resubmission; Table 20, p118 of the ELEVATE-TN interim clinical study report.

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

Bold indicates statistically significant results.

- 6.25 At a median duration of follow-up of 28.3 months, time to next treatment was statistically significantly longer among patients in the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms compared to the chlorambucil + obinutuzumab arm (median not reached in any arm; HR = 0.14 [95% CI: 0.08, 0.26] for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab; HR = 0.24 [95% CI: 0.15, 0.40] for acalabrutinib monotherapy versus chlorambucil + obinutuzumab). At the interim analysis, 25% of patients in the chlorambucil + obinutuzumab treatment arm had crossed over to receive acalabrutinib treatment (39% at the September 2020 data cut). The availability of crossover treatment with acalabrutinib monotherapy for patients with confirmed disease progression in the chlorambucil + obinutuzumab arm may have influenced the time to next treatment in the chlorambucil + obinutuzumab arm.
- 6.26 No new data for health-related quality of life outcomes were presented in 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.
- 6.27 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.
- 6.28 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. The ESC considered that it would be informative for the PBAC to know when updated QoL results would be available. No further information was provided in the pre-PBAC response.

Comparative harms

6.29 Table 9 summarises the results of safety outcomes for the ELEVATE-TN trial.

Table 9: Summary of adverse events for the ELEVATE-TN trial at the February 2019 interim analysis and for the September 2020 data cut

	Feb 2019 data cut			Sep 2020 data cut		
	ACAL + OBI (N=178)	ACAL (N=179)	CHL + OBI (N=169)	ACAL + OBI (N=178)	ACAL (N=179)	CHL + OBI (N=169)
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)	47.0 (1.7-59.2)	46.9 (0.1-59.4)	46.2 (0.0-58.4)
Grade ≥3 AE, n (%)	125 (70.2)	89 (49.7)	118 (69.8)	132 (74.2)	93 (51.9)	116 (68.6) ^a
Serious AE, n (%)	69 (38.8)	57 (31.8)	37 (21.9)	85 (47.8)	70 (39.1)	37 (21.9)
Discontinuation due to AE, n (%)						
- Acalabrutinib	19 (10.7)	17 (9.5)	-	NR	NR	NR
- Obinutuzumab	11 (6.2)	-	10 (5.9)	NR	NR	NR
- Chlorambucil	-	-	24 (14.2)	NR	NR	NR
AE leading to death, n (%)	4 (2.8)	6 (3.4)	4 (2.4)	5 (2.8)	11 (6.1)	4 (2.4)
Treatment-related AE, n (%)	144 (80.9)	118 (65.9)	154 (91.1)	NR	NR	NR
Any AE, n (%)	171 (96.1)	170 (95.0)	167 (98.8)	176 (98.8)	173 (96.6)	167 (98.8)
Any AE incidence ≥25%, n (%)						
- Diarrhoea	69 (38.8)	62 (34.6)	36 (21.3)	73 (41.0)	72 (40.2)	36 (21.3)
- Headache	71 (39.9)	66 (36.9)	20 (11.8)	71 (39.9)	68 (38.0)	20 (11.8)
- Neutropenia	56 (31.5)	19 (10.6)	76 (45.0)	60 (33.7)	22 (12.3)	76 (45.0)
- Fatigue	50 (28.1)	33 (18.4)	29 (17.2)	50 (28.1)	39 (21.8)	30 (17.8)
- Arthralgia	39 (21.9)	28 (15.6)	8 (4.7)	47 (26.4)	35 (19.6)	8 (4.7)
- Cough	39 (21.9)	33 (18.4)	15 (8.9)	46 (25.8)	40 (22.3)	15 (8.9)
- Upper respiratory tract infection	38 (21.3)	33 (18.4)	14 (8.3)	44 (24.7)	46 (25.7)	16 (9.5)
- Nausea	36 (20.2)	40 (22.3)	53 (31.4)	41 (23.0)	41 (22.9)	53 (31.4)
- Infusion-related reaction	24 (13.5)	0	67 (39.6)	25 (14.0)	0	68 (40.2)
Grade ≥3 AE incidence >2%, n (%)						
- Neutropenia	53 (29.8)	17 (9.5)	70 (41.4)	55 (30.9)	20 (11.2)	70 (41.4)
- Thrombocytopenia	15 (8.4)	5 (2.8)	20 (11.8)	NR	NR	NR
- Anaemia	10 (5.6)	12 (6.7)	12 (7.1)	NR	NR	NR
- Febrile neutropenia	3 (1.7)	2 (1.1)	9 (5.3)	NR	NR	NR
- Diarrhoea	8 (4.5)	1 (0.6)	3 (1.8)	9 (5.1)	1 (0.6)	3 (1.8)
- Upper respiratory tract infection	4 (2.2)	0	1 (0.6)	4 (2.2)	0	1 (0.6)
- Pneumonia	10 (5.6)	4 (2.2)	3 (1.8)	NR	NR	NR
- Infusion-related reaction	4 (2.2)	0	9 (5.3)	5 (2.8)	0	10 (5.9)
- ALT increased	5 (2.8)	1 (0.6)	3 (1.8)	NR	NR	NR
- Neutrophil count decreased	2 (1.1)	0	5 (3.0)	NR	NR	NR
- Tumour lysis syndrome	2 (1.1)	0	13 (7.7)	NR	NR	NR
- Syncope	4 (2.2)	2 (1.1)	1 (0.6)	NR	NR	NR
- Hypertension	5 (2.8)	4 (2.2)	5 (3.0)	NR	NR	NR

Source: Table 2.24, pp106-107; Table 2.25, p108; Table 2.26, pp108-109; Table 2.27, p109 of the resubmission; Supplemental Table 3 of Attachment 10 of the resubmission.

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

^a The number reported for the September 2020 data cut was smaller than the number reported for the February 2019 data cut.

- 6.30 Almost all patients in each treatment arm experienced at least one treatment-emergent adverse event. At the September 2020 data cut, serious adverse events were higher in the acalabrutinib + obinutuzumab (48%) and acalabrutinib monotherapy (39%) arms, compared to the chlorambucil + obinutuzumab arm (22%). Grade ≥ 3 adverse events were higher in the acalabrutinib + obinutuzumab (74%) and chlorambucil + obinutuzumab arms (69%) compared to the acalabrutinib monotherapy arm (52%). Results for treatment-related adverse events were not available for the September 2020 data cut.
- 6.31 The most commonly reported adverse events in the acalabrutinib + obinutuzumab arm (>25%) were diarrhoea (41%), headache (40%), neutropenia (34%), fatigue (28%), arthralgia (26%) and cough (26%). The most commonly reported adverse events in the acalabrutinib monotherapy arm (>25%) were diarrhoea (40%), headache (38%) and upper respiratory tract infection (26%).
- 6.32 The PBAC previously noted that the difference in treatment duration (acalabrutinib is given until disease progression; chlorambucil is given for 24 weeks) likely impacted the overall numbers of adverse events (paragraph 7.8, acalabrutinib, PSD, July 2020 PBAC meeting).
- 6.33 Overall, in terms of safety, the PBAC had previously considered that acalabrutinib monotherapy was likely to be superior compared to chlorambucil + obinutuzumab, and acalabrutinib + obinutuzumab was likely to result in similar safety outcomes compared to chlorambucil + obinutuzumab. However, the PBAC had also noted that both acalabrutinib monotherapy and acalabrutinib + obinutuzumab were associated with a higher incidence of serious adverse events compared to chlorambucil + obinutuzumab (paragraph 7.8, acalabrutinib, PSD, July 2020 PBAC meeting).

Benefits/harms

- 6.34 On the basis of the direct evidence presented in the resubmission, for every 100 patients treated with acalabrutinib monotherapy in comparison with chlorambucil + obinutuzumab:
- Approximately 53 additional patients will remain progression free at four years.
 - At a median follow-up of 46.9 months, approximately 30 fewer patients will experience life-threatening or severe neutropenia and approximately 6 fewer patients will experience a life-threatening or severe infusion-related reaction.
 - At a median follow of 28.3 months, approximately 9 fewer patients will experience life-threatening or severe thrombocytopenia and approximately 8 fewer patients will experience life-threatening or severe tumour lysis syndrome.

Clinical claim

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

and venetoclax + obinutuzumab, or patients who become intolerant to venetoclax + obinutuzumab.

- 6.36 The PBAC had previously considered that this claim was reasonable for the broader population of patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy, but the magnitude of the benefit was uncertain due to the immaturity of the data.
- 6.37 The PBAC considered that the overall claim of superior comparative effectiveness was reasonable overall for the narrower population proposed in the resubmission. The PBAC was now more confident this claim was reasonable in relation to PFS, noting that the more mature data in the resubmission with follow-up over approximately four years showed consistency of effect. At the same time, it remained of the view that it would be inappropriate to model an overall survival gain in the economic evaluation as this data remained immature and there may not be a difference over the longer term given subsequent lines of effective therapy are available.
- 6.38 The PBAC remained of the view that the claim of superior comparative safety was likely reasonable, noting that although acalabrutinib was associated with a higher incidence of serious adverse events, Grade ≥ 3 adverse events were lower, and the longer duration of treatment with acalabrutinib would be expected to have impacted the overall number of adverse events.

Economic analysis

- 6.39 The resubmission presented a modelled economic evaluation of acalabrutinib monotherapy versus chlorambucil + obinutuzumab, in patients with previously untreated CLL/SLL who are unsuitable for treatment with fludarabine-based chemoimmunotherapy and venetoclax + obinutuzumab, or who permanently discontinue treatment with venetoclax + obinutuzumab due to intolerance. The economic evaluation was presented as a stepped cost-effectiveness/cost-utility analysis.
- 6.40 A partitioned survival design, using the overall survival and progression-free survival curves from the ELEVATE-TN trial, was implemented to distribute patients between model health states. The economic model included in the July 2020 submission was a Markov model with six health states (progression-free on-treatment, progression-free off-treatment, drug holiday, second-line treatment, best supportive care and dead), and explicitly modelled outcomes for second-line therapies using data from published relapsed/refractory CLL trials. The PBAC had previously considered a partitioned survival model for venetoclax + obinutuzumab, which contained an additional health state and additional utility states (March and July 2020 PBAC meetings).

Table 10: Key components of the economic evaluation

Component	Description
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.
Methods used to generate results	Partitioned survival analysis
Treatments	<p>First-line treatments used in the model were based on the regimens used in the ELEVATE-TN trial (acalabrutinib monotherapy, chlorambucil + obinutuzumab). Duration of use for acalabrutinib was based on drug exposure data from the ELEVATE-TN trial (derived from extrapolated time to treatment discontinuation data). Duration of use for chlorambucil + obinutuzumab was based on an assumed six cycles of treatment, adjusted for progression-free survival.</p> <p>The resubmission assumed that second-line therapy for acalabrutinib patients would consist of idelalisib + rituximab and second-line therapy for chlorambucil + obinutuzumab patients would consist of ibrutinib monotherapy. Treatment duration for ibrutinib and idelalisib + rituximab was estimated from time to progression data for the RESONATE and ASCEND trials.</p>
Health states	Progression-free; progressed disease; dead.
Cycle length	1 month
Allocation to health states	<p>Kaplan-Meier estimates of progression-free survival and overall survival were sourced from the ELEVATE-TN trial and extrapolated using parametric functions.</p> <p>Progression-free survival was extrapolated using an exponential function for the acalabrutinib arm, and a log-logistic function for the chlorambucil + obinutuzumab arm.</p> <p>No difference in overall survival was assumed between treatment arms and was based on the overall survival results for the chlorambucil + obinutuzumab arm, extrapolated using an exponential function.</p>
Health state utilities	<p>Pre-progression utility values (0.817) based on mean utility value across all treatment arms in the ELEVATE-TN trial (at the interim analysis).</p> <p>Post-progression utility (0.657) derived from a published utility study of CLL from the perspective of the UK general public (Kosmas 2015), re-anchored to the oral initial therapy state. The ESC noted that updated utilities were not available from ELEVATE-TN. For the progressed disease state, a mean utility across all treatment arms was reported as 0.804 (n=45) at the interim analysis.</p> <p>Adverse event disutility values were estimated from venetoclax + rituximab NICE submission [ID1097], Nafees et al. (2008), and Wehler et al. (2018).</p>

Component	Description
Costs	<p>Acalabrutinib drug cost based on the proposed effective price including the effects of both an SPA rebate and an RSA treatment cap. Drug cost for obinutuzumab estimated from published DPMA assuming an SPA rebate. Drug cost for idelalisib estimated from published DPMQ assuming both an SPA rebate and an RSA treatment cap. Drug cost for ibrutinib based on effective AEMP recorded in relapsed/refractory CLL deed and assuming an RSA treatment cap. Drug costs for rituximab and chlorambucil based on published DPMQs.</p> <p>Premedication costs for chlorambucil + obinutuzumab (paracetamol, loratadine, dexamethasone) based on EviQ treatment protocol. Tumour lysis syndrome prophylaxis cost for obinutuzumab based on cost per patient reported in the venetoclax July 2020 resubmission Public Summary Document.</p> <p>Administration costs for obinutuzumab and rituximab based on MBS Item 13950 for private hospital use and AR-DRG Round 23 (2018-19) for public hospital use, weighted based on PBS dispensing data. The cost assumed in the model for public hospital chemotherapy administration were substantially higher than the private hospital chemotherapy administration costs (\$546.28 versus \$111.40) but did not have a substantial impact on the modelled results.</p> <p>Adverse event costs estimated by mapping adverse events reported in the ELEVATE-TN trial to AR-DRG items.</p> <p>Disease management costs based on costs for progression-free and progressed states included in the July 2020 venetoclax resubmission Public Summary Document.</p> <p>Terminal care costs derived from Langton et al. (2016), based on health service use and costs in the last six months of life in NSW elderly Australian Government Department of Veterans' Affairs veterans with a history of cancer.</p>

Source: Section 3, pp145-175 of the resubmission.

AEMP, approved ex-manufacture price; AR-DRG, Australian Refined Diagnosis Related Group; CLL, chronic lymphocytic leukaemia; DPMA, dispensed price for maximum amount; DPMQ, dispensed price for maximum quantity; RSA, risk-sharing agreement; SPA, special pricing arrangement; UK, United Kingdom.

- 6.41 The model was based on the full trial population results for the ELEVATE-TN trial. As the model was based on a partitioned survival approach, treatment effectiveness reflected the first- and subsequent-line treatments used by patients in the ELEVATE-TN. Results for the ELEVATE-TN trial were relatively immature, with median progression-free survival and overall survival not reached in the acalabrutinib arm.
- 6.42 The resubmission applied costs associated with subsequent treatments based on subsequent treatments assumed to be used in the proposed PBS population (i.e. idelalisib + rituximab for the acalabrutinib arm, and ibrutinib monotherapy for the chlorambucil + obinutuzumab arm).
- 6.43 The model included costs and disutilities associated with Grade 3 and 4 adverse events which occurred in $\geq 2\%$ of patients in either the acalabrutinib or chlorambucil + obinutuzumab arms of the ELEVATE-TN trial. Costs and disutilities were derived based on reported adverse event incidences. However, the evaluation considered it would be more appropriate to derive adverse event costs and disutilities using adverse event rates, given that individuals may experience a single adverse event multiple times. There are differences in adverse event profiles between the included subsequent therapies (i.e. idelalisib + rituximab and ibrutinib) that were not captured in the model.

6.44 Key drivers of the economic model are summarised in the table below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Time horizon	The base case analysis employed a 15-year time horizon. The resubmission noted that a 15-year time horizon was included in the November 2010 fludarabine + cyclophosphamide + rituximab submission (paragraph 10, rituximab, Public Summary Document, November 2010 PBAC meeting), and argued that a time horizon longer than 10 years is required to capture all of the benefits from treatment with acalabrutinib. The PBAC had previously considered a time horizon of 10 years to be appropriate when considering submissions for venetoclax + obinutuzumab (March 2020), chlorambucil + obinutuzumab (July 2014) and ibrutinib (November 2017). The PSCR maintained that a 15-year time horizon was appropriate as previously considered by ESC (ESC had “considered that a time horizon of 15 years [rather than 20 years in the base case] would mitigate some of the uncertainty in the model...” (para 6.63, acalabrutinib PSD, July 2020 meeting). The PSCR argued that a 15-year time horizon was needed to capture all of the benefits from the longer duration of treatment with acalabrutinib, compared to the fixed shorter duration treatment of chlorambucil + obinutuzumab.	Moderate, favours acalabrutinib
Progression-free survival extrapolation	Progression-free survival data for acalabrutinib and chlorambucil + obinutuzumab corresponding to a median duration of follow-up of 46.9 months was extrapolated to 15 years using parametric functions. It was unclear whether the assumed progression-free survival function for acalabrutinib would reflect progression-free survival in clinical practice. The PBAC had previously noted that longer time horizons in patients unsuitable for a purine analogue may be unreliable due to the immaturity of available clinical trial data and the fragility of patient populations (patients >70 years of age who will likely have comorbidities; paragraph 7.9, ibrutinib, Public Summary Document, November 2017 PBAC meeting).	Moderate, favours acalabrutinib
Partitioned survival analysis	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 evaluation considered 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 over time, given multiple lines of subsequent therapy, and periods of disease remission. The PSCR reiterated that the simplified 3 health state partitioned survival model (with survival outcomes modelled directly from the ELEVATE-TN trial) was implemented in response to feedback from ESC and PBAC relating to the previous 6 health state Markov transition model. Moreover, in the current model, “it was conservatively assumed that acalabrutinib patients would receive no overall survival gain relative to chlorambucil + obinutuzumab despite some divergence in ELEVATE-TN”.	Unclear impact
Subsequent treatment costs	Subsequent therapy costs were derived based on the assumption that patients in the acalabrutinib arm would receive subsequent treatment with idelalisib with rituximab, and patients in the chlorambucil arm would receive subsequent treatment with ibrutinib monotherapy. While the intention of this assumption was to model costs for the PBS population (who are considered unsuitable for venetoclax + obinutuzumab) based on available PBS-listed treatments, this resulted in a mismatch between assumed use and actual use in the ELEVATE-TN trial. Additionally, many patients who are considered unsuitable for first-line treatment with venetoclax + obinutuzumab are likely to be treated with later-line venetoclax + rituximab (depending on the underlying reasons for being unsuitable for venetoclax + obinutuzumab, and in the context of limited available remaining treatment options). The resubmission estimated the impact of risk-sharing arrangements for idelalisib and ibrutinib by assuming maximum treatment duration caps of 12 and 26 months for idelalisib and ibrutinib, respectively. The assumed maximum treatment caps may not reflect the actual risk-sharing arrangements in place.	Unclear impact

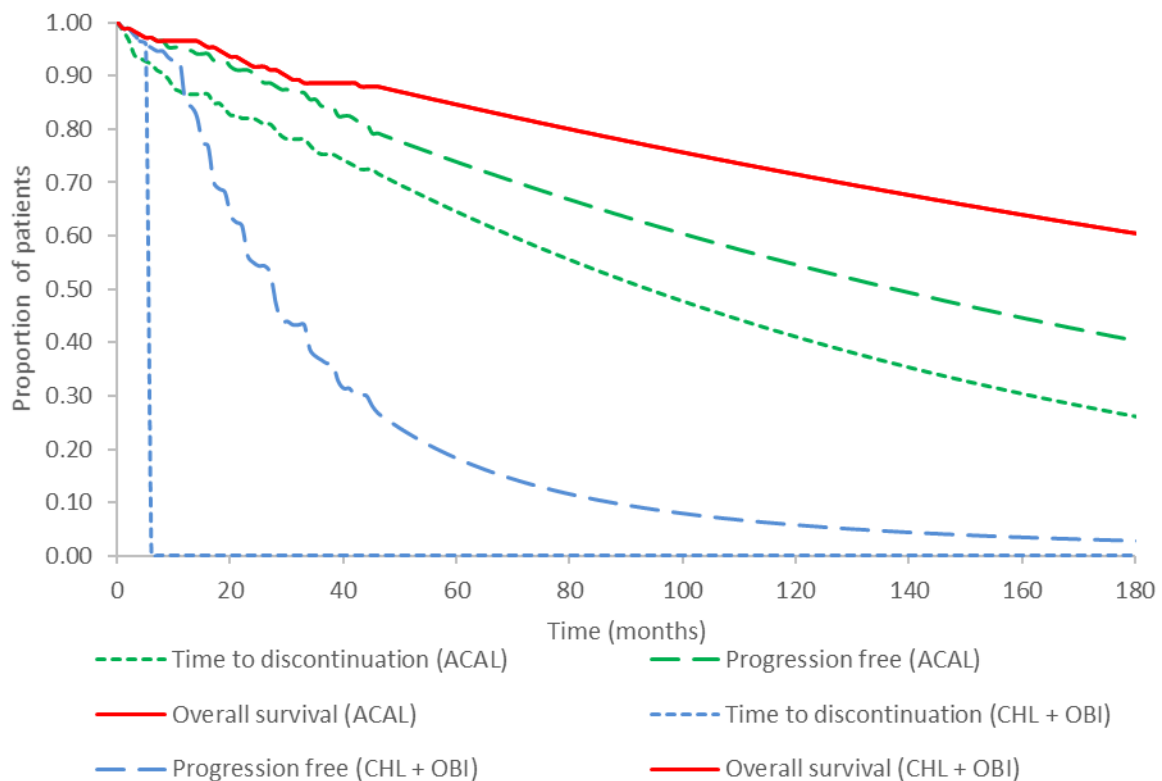
Source: Constructed during the evaluation.

CLL, chronic lymphocytic leukaemia.

6.45 Utility values used in the economic evaluation were informed by Kosmas et al. (2015), re-anchored to the oral initial therapy state as these were previously considered more appropriate by the PBAC (para. 7.10, acalabrutinib PSD, July 2020). However, as noted in the table above, the evaluation expressed concerns that assumed progressed disease state cost and utility may not adequately reflect the cost and quality of life experienced by patients with CLL over time. The PSCR presented the results of a sensitivity analysis that assumed a progressed disease utility of 0.651 (adjusting the 0.657 used in the resubmission base case, to account for relative proportion of time spent in three time periods captured in the progressive disease state in the model: treatment holiday between 1L progression and start of 2L treatment (progressed but well), progression-free survival associated with 2L treatment, and 2L treatment relapse/BSC, in which no other treatment options exist). This resulted in a cost per QALY gained of \$55,000 to < \$75,000 (compared with \$55,000 to < \$75,000 per QALY gained in the resubmission the base case). Thus, the PSCR argued, the value used in the base case model did not bias the analysis towards acalabrutinib. The ESC considered that it would be informative for the PBAC to know when updated utilities from ELEVATE-TN would be available.

6.46 Model traces for the acalabrutinib and chlorambucil + obinutuzumab arms are presented in the figure below.

Figure 4: Model traces for the acalabrutinib and chlorambucil + obinutuzumab arms



Source: 'Attachment 23_ACA_CEA_FINAL' Excel workbook, Attachment 23 of the resubmission.

ACAL, acalabrutinib; CHL, chlorambucil; OBI, obinutuzumab.

- 6.47 The model traces indicated that approximately 60% of patients in the acalabrutinib arm were alive at 15 years, with approximately 40% of patients remaining progression-free. Comparatively, approximately 60% of patients in the chlorambucil + obinutuzumab arm were alive at 15 years, with <5% of patients remaining progression-free. The July 2020 model results indicated that approximately 50% of patients in the acalabrutinib monotherapy arm and 30% of patients in the chlorambucil + obinutuzumab arm were alive at 15 years.
- 6.48 The results of the modelled economic evaluation using the estimated effective prices for obinutuzumab and idelalisib are summarised in Table 12. The results of the economic evaluation using the actual effective prices of obinutuzumab, ibrutinib and idelalisib were presented in a Committee-in-Confidence section.

Table 12: Results of the economic evaluation

Component	Acalabrutinib	Chlorambucil + obinutuzumab	Increment
Costs (\$)		\$152,778	
QALYs	6.85	6.12	0.73
Incremental cost per QALY gained			¹

Source: the resubmission.

QALY, quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

- 6.49 Based on the economic model, treatment with acalabrutinib was associated with an incremental cost per QALY gained of \$55,000 to < \$75,000 compared to chlorambucil + obinutuzumab.
- 6.50 The difference in health outcomes between treatment arms was driven by the longer time in the progression-free health state and shorter time in the progressed health state in the acalabrutinib arm compared to the chlorambucil + obinutuzumab arm. No difference in overall survival was modelled.
- 6.51 The difference in total cost between treatment arms was primarily driven by higher first-line treatment costs in the acalabrutinib arm (due to the higher cost of acalabrutinib and longer time spent in the progression-free health state) compared with the chlorambucil + obinutuzumab arm, which were partly offset by lower second-line treatment costs in the acalabrutinib arm (due to the lower estimated cost of idelalisib + rituximab treatment compared to ibrutinib treatment, and the shorter time spent in the progressed disease state) compared to the chlorambucil + obinutuzumab arm (as shown in table below).

Table 13: Disaggregated summary of cost impacts in the economic evaluation

Type of resource item	Acalabrutinib (\$)	Chlorambucil + obinutuzumab	Incremental cost	% of total incremental cost
First-line treatment		\$19,118		290.1%
TLS prophylaxis		\$1,222	-	-2.7%
Pre-medications		\$35	-	-0.1%
First-line treatment administration		\$2,291	-	-5.1%
Subsequent treatment (including administration)		\$72,574	-	-122.1%
Disease management		\$42,962	-	-55.9%
Adverse events		\$3,562	-	-4.1%
Terminal care		\$11,014		0.0%
Total costs		\$152,778		100.0%

Source: the resubmission.

TLS, tumour lysis syndrome.

6.52 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in the table below.

Table 14: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER
Base case	██████████	0.73	██████████ ¹
Time horizon (base case 15 years)			
10 years	██████████	0.54	██████████ ²
20 years	██████████	0.84	██████████ ³
Acalabrutinib arm PFS extrapolation (base case: exponential function)			
Weibull ^a	██████████	0.69	██████████ ¹
Log-Normal ^a	██████████	0.78	██████████ ³
Log-Logistic ^a	██████████	0.73	██████████ ¹
Gompertz	██████████	0.57	██████████ ⁴
Generalised Gamma ^a	██████████	0.61	██████████ ²
Acalabrutinib treatment duration (base case: time to treatment discontinuation data extrapolated using an exponential function with 48-month cap)			
Acalabrutinib progression-free survival curve used	██████████	0.73	██████████ ²
Weibull ^a	██████████	0.73	██████████ ¹
Log-normal ^a	██████████	0.73	██████████ ¹
Log-logistic ^a	██████████	0.73	██████████ ¹
Gompertz ^a	██████████	0.73	██████████ ¹
Generalised gamma ^a	██████████	0.73	██████████ ¹
Remove cycle cap for acalabrutinib	██████████	0.73	██████████ ⁵
Utilities (base case: progression-free utility of 0.817; progressed disease utility of 0.657; adverse event disutilities included)			
Progression-free utility increased to 0.867 ^a	██████████	0.95	██████████ ³
Progression-free utility decreased to 0.767 ^a	██████████	0.50	██████████ ²
Progressed disease utility increased to 0.707 ^a	██████████	0.50	██████████ ²
Progressed disease utility decreased to 0.607 ^a	██████████	0.95	██████████ ³
Adverse event disutilities removed ^a	██████████	0.72	██████████ ¹
Subsequent treatment costs (base case: ██████% of patients receive subsequent treatment; obinutuzumab – ██████% rebate on published AEMP; ibrutinib – effective DPMQ with 24-month cap; idelalisib – ██████% rebate on published AEMP with 12-month cap; rituximab – published DPMA; chlorambucil – published DPMQ; includes adjustment for dose intensity)			
Proportion receiving subsequent treatment: acalabrutinib and chlorambucil + obinutuzumab arms: 75% ^b	██████████	0.73	██████████ ²
Remove cycle cap for ongoing second-line therapies (ibrutinib, idelalisib) ^a	██████████	0.73	Acalabrutinib dominant
Remove dose intensity for all treatments ^a	██████████	0.73	██████████ ¹
Other costs (base case: health state, adverse event, terminal care costs and TLS prophylaxis costs included)^a			
Health state costs increased by 50%	██████████	0.73	██████████ ⁶
Health state costs decreased by 50%	██████████	0.73	██████████ ²
Health state costs removed	██████████	0.73	██████████ ⁴
Adverse event costs removed	██████████	0.73	██████████ ¹
Terminal care costs removed	██████████	0.73	██████████ ¹
TLS prophylaxis costs removed	██████████	0.73	██████████ ¹
Discount rate (base case: 5% for benefits and costs)			
0% for costs and benefits	██████████	1.05	██████████ ⁶
3.5% for costs and benefits	██████████	0.81	██████████ ³

Source: Compiled using the 'Attachment 23_ACA_CEA_FINAL' Excel Workbook, Attachment 23 of the resubmission.

AEMP, approved ex-manufacturer price; DPMQ, dispensed price for maximum quantity.

^a Sensitivity analyses done during the evaluation.

^b Added for the ESC advice. Affects costs only. Due to the use of a partitioned survival approach, effectiveness outcomes are dictated by the extrapolated overall survival and progression-free survival curves from the ELEVATE-TN and are not impacted by changes in

subsequent treatment utilisation.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$45,000 to < \$55,000

⁴ \$95,000 to < \$115,000

⁵ \$255,000 to < \$355,000

⁶ \$35,000 to < \$45,000

6.53 The model was most sensitive to the time horizon, choice of parametric function to extrapolate progression-free survival for acalabrutinib, inclusion of assumed treatment duration caps for acalabrutinib and second-line therapies, the assumed progression-free and progressed disease health state utilities, and the included health state costs. The ESC noted that the model result was sensitive to key inputs including (i) the model time horizon (increasing to \$75,000 to < \$95,000 per QALY gained with a 10-year horizon), (ii) the extrapolated progression free survival curve (increasing to \$95,000 to < \$115,000 per QALY gained for the Gompertz extrapolation, which was the second-best fitting curve), (iii) the utility values (increasing to \$75,000 to < \$95,000 per QALY gained with a progressed utility of 0.707, which ESC noted was still lower than the estimate of 0.804 sourced from the interim ELEVATE-TN trial analysis). The ESC further noted that removing the acalabrutinib treatment cap increased the ICER to \$255,000 to < \$355,000 per QALY gained, and therefore if the use of acalabrutinib were less than the estimates used to inform the RSA treatment caps, then the actual ICERs would be higher than those estimated in Table 14.

6.54 The pre-PBAC response:

- Considered that the Gompertz extrapolation was an outlier, noting that the AIC/BIC statistics generated by the log-logistic and Weibull functions were similar to the Gompertz, but generated similar ICERs/QALY gained as the resubmission base case.
- Maintained the appropriateness of a 15-year time horizon, given the sustained PFS benefit demonstrated in the later data cut of the ELEVATE-TN trial.
- Recognised that the treatment cap would only be effective if utilisation estimates closely reflected those predicted in the resubmission.

Drug cost/patient/year

6.55 The estimated drug cost for acalabrutinib was \$ [REDACTED] per patient per year (based on < 500 scripts using the effective DPMQ \$ [REDACTED] for 28 days treatment and assuming a dose intensity of 96.8%). The resubmission estimated a maximum cost of \$ [REDACTED] per patient for acalabrutinib based on a risk-sharing agreement cap of 48 months. The estimated drug cost per patient per course for acalabrutinib exclusive of the 48-month treatment cap was \$ [REDACTED] (based on < 500 scripts per year, the effective DPMQ of \$ [REDACTED] for 28 days treatment, a dose intensity of 96.8%, and an estimated mean treatment duration of 10.4 years derived from the ELEVATE-TN time to treatment discontinuation curve extrapolated using an exponential function).

- 6.56 The estimated drug cost for obinutuzumab was \$19,870 for a single six-month treatment course (based on 8 infusions, an estimated effective weighted public/private hospital DPMA of \$2,647.87, and a dose intensity of 93.8%).
- 6.57 The estimated drug cost for chlorambucil was \$1,070 for a single six-month treatment course (based on six cycles/12 doses, a published DPMQ of \$135.34 per pack, a dose intensity of 83.4%, and average dose of 39.5 mg). The cost of chlorambucil appeared to be overestimated in the resubmission, as the calculation was based on a DPMQ of \$135.34 for 25 tablets, whereas the PBS specifies a DPMQ of \$135.34 for 100 tablets.
- 6.58 The estimated drug costs per patient for acalabrutinib monotherapy and chlorambucil + obinutuzumab combination therapy are summarised in Table 15.

Table 15: Annual drug costs acalabrutinib and chlorambucil + obinutuzumab

Treatment regimen	First year (\$)	Subsequent years ^a (\$)
Acalabrutinib monotherapy		
Chlorambucil + obinutuzumab	\$20,940	\$0

Source: 'INDEX Tx costs' worksheet of the 'Attachment 23_ACA_CEA_FINAL' Excel workbook.

^aThe resubmission proposed a risk-sharing arrangement for acalabrutinib in which the cost to the Australian Government would be capped at a maximum of 48 months.

Estimated PBS usage & financial implications

- 6.59 This resubmission was not considered by DUSC. The resubmission used a mixed epidemiological/market share approach.
- 6.60 The sources of data used in the financial estimates are presented in the table below.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident CLL patients	Incidence of 7.0/100,000 (crude rate; 2021 AIHW estimate) applied to ABS Australian population projections (Series B 3222.0).	The estimates were based on the age-standardised CLL incidence, which was lower than the age-specific incidence (projected to be 8.6 cases per 100,000 in 2017; AIHW, 2021).
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).	The resubmission did not provide additional justification.
Proportion of first-line eligible patients who are unsuitable for a purine analogue	65%. Based on venetoclax PSD July 2020 (clinician advice).	The resubmission did not provide additional justification.
Proportion unsuitable for venetoclax + obinutuzumab	14%. Sponsor assumption (informed by clinician advice that 30% of patients would be unsuitable or intolerant for venetoclax + obinutuzumab, and given 16% were assumed to be intolerant, i.e. 30%-16%=14%).	This estimate was highly uncertain as unsuitability for venetoclax + obinutuzumab was not clearly defined in the proposed restriction, and if it were defined, is likely to be based on highly subjective criteria.
Proportion intolerant of venetoclax + obinutuzumab	16%. Sponsor assumption. The resubmission claimed that the number of patients treated with acalabrutinib would be approximately 16% of the eligible venetoclax + obinutuzumab population, based on the proportion of patients who discontinued treatment due to adverse events in the CLL-14 trial (Fischer et al., 2019).	The estimate appeared to be based on the proportion of patients who discontinued at least one treatment component due to an adverse event. Patients who are intolerant to obinutuzumab may continue treatment with venetoclax.

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Parameter	Value applied and source	Comment
Uptake of acalabrutinib among venetoclax + obinutuzumab unsuitable patients	Yr 1-6: 100%. Sponsor assumption.	Uptake may be overestimated given that not all patients may elect treatment.
Choice of subsequent therapy	Assumed that patients treated with acalabrutinib in the first-line setting would receive idelalisib + rituximab and patients treated with chlorambucil + obinutuzumab would receive ibrutinib monotherapy (as a proxy for available BTK inhibitors – ibrutinib and acalabrutinib).	A substantial proportion of patients may be able to receive treatment with venetoclax + rituximab as a subsequent therapy.
Proportion of acalabrutinib-treated patients initiating subsequent treatment with idelalisib + rituximab each year.	Y1: 2.65%, Y2: 2.12%, Y3: 3.07%, Y4: 2.96%, Y5: 2.30%, Y6: 2.17%. Time to disease progression data for the acalabrutinib arm of the ELEVATE-TN trial fitted with a log-logistic function was used to estimate the number of patients each year with disease progression.	The approach used to estimate changes in ibrutinib and obinutuzumab script counts (based on a market share approach using PBS dispensing data) differed from the approach used to estimate the number of acalabrutinib and idelalisib and rituximab scripts (epidemiological approach adjusted for trial-based utilisation).
Proportion of chlorambucil + obinutuzumab-treated patients initiating subsequent treatment with ibrutinib monotherapy each year	Y1: 7.58%, Y2: 14.94%, Y3: 9.12%, Y4: 5.75%, Y5: 3.50%, Y6: 2.27%. Time to disease progression data for the chlorambucil + obinutuzumab arm of the ELEVATE-TN trial fitted with an exponential function was used to estimate the number of patients each year with disease progression.	The approach used to estimate changes in ibrutinib and obinutuzumab script counts (based on a market share approach using PBS dispensing data) differed from the approach used to estimate the number of acalabrutinib and idelalisib and rituximab scripts (epidemiological approach adjusted for trial-based utilisation).
Obinutuzumab CLL scripts (2020)	2,706 scripts. Medicare Statistics PBS Item reports for 10407R and 10418H (January 2020 to December 2020)	-
Chlorambucil scripts (2020)	2,706 scripts. Assumed 1 chlorambucil script for each obinutuzumab script.	-
Ibrutinib scripts (2020)	13,646 scripts. Medicare Statistics PBS Item report for 11213E (January 2020 to December 2020)	-
Obinutuzumab, ibrutinib and chlorambucil script growth	2021: 1.65%, 2022: 1.62%, 2023: 1.57%, 2024: 1.53%, 2025: 1.48%, 2026: 1.44%, 2027: 1.39%. Assumed annual growth from 2020 levels based on the percent increase in incident CLL patients each year, assuming an annual incidence of 7.0 per 100,000 population.	The availability of additional treatments on the PBS may lead to growth of the overall CLL market.
Acalabrutinib treatment duration	40.28 months. Based on the extrapolated time to treatment discontinuation data for the acalabrutinib arm of the ELEVATE-TN trial, adjusted for the proposed 48-month maximum treatment cap.	This assumption differed from the assumptions around treatment duration for idelalisib, which was based on time to progression.
Idelalisib treatment duration	12 months. Assumed that all patients receive 12 months of treatment, based on the assumption that idelalisib is subject to an RSA with a 12-month maximum treatment cap.	The assumed maximum treatment cap may not reflect the actual RSA parameters. Refer to Committee-In-Confidence section of the ESC advice.

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Parameter	Value applied and source	Comment
Proportion of ibrutinib scripts replaced	19.5%. Assumed that 65% of ibrutinib scripts attributable to patients not suitable for fludarabine-based treatment and 30% of ibrutinib use is following chlorambucil + obinutuzumab (70% following venetoclax + obinutuzumab). Calculated as 65% x 30% = 19.5%.	The approach used to estimate changes in ibrutinib and obinutuzumab script counts (based on a market share approach using PBS dispensing data) differed from the approach used to estimate the number of acalabrutinib and idelalisib scripts (epidemiological approach adjusted for trial-based utilisation). It is unclear whether the two approaches produced consistent results.
Acalabrutinib price	\$ [REDACTED]. Requested effective DPMQ.	-
Chlorambucil price	\$135.34. Published DPMQ.	-
Obinutuzumab price	\$2,647.89 per script. Based on split between Item 10407R and 10418H (38%:62% public:private), January to December 2020. The resubmission assumed an effective price at a 50% discount to the published price.	Estimates based on the effective price of obinutuzumab are presented in the Committee-In-Confidence section of the ESC advice.
Ibrutinib price	Derived from the effective AEMP for ibrutinib specified in the relapsed/refractory CLL deed.	-
Idelalisib price	\$2,770.10. PBS item 11162L. The resubmission noted that idelalisib is subject to an SPA and estimated the effective price to be 50% lower than the published price.	Estimates based on the effective price of idelalisib are presented in the Committee-In-Confidence section of the ESC advice.
Rituximab price	\$1,366.43. Based on split between Item 4614W and 7257Y (34.9%:65.1% public:private), January to December 2020.	This appeared reasonable.
Allopurinol price	\$17.01. Published DPMQ	-
Intravenous infusion of cytotoxic chemotherapy	\$89.12. MBS Item 13950 (parenteral administration of one or more antineoplastic agents by or on behalf of a specialist or consultant physician).	Assumed 80% of the scheduled fee.

Source: Table 4.1, p187; Table 4.2, p189 of the resubmission; 'Attachment 24_ACA_BIM_Section 4_Final' Excel workbook, Attachment 24 of the resubmission.

ABS, Australian Bureau of Statistics; AEMP, approved ex-manufacture price; BTK, Bruton's Tyrosine Kinase; CLL, chronic lymphocytic leukaemia; DPMQ, dispensed price for maximum quantity; MBS, Medicare Benefits Scheme; PBS, pharmaceutical Benefits Scheme; SPA, special pricing arrangement; Yr, Year.

6.61 Table 17 presents the estimated net cost to the PBS/RPBS of listing acalabrutinib. Estimates using effective prices of all drugs and are presented in the Committee-In-Confidence section.

Table 17: Estimated number of treated patients and the cost of acalabrutinib to the PBS/RPBS.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Australian population	26,727,025	27,147,199	27,562,195	27,970,435	28,372,315	28,765,734
CLL incidence (7.0/100,000)	1,871	1,900	1,929	1,958	1,986	2,014
Initiate in year of diagnosis (30%)	561	570	579	587	596	604
Initiate 1 year after diagnosis	138	140	143	145	147	149
Initiate 2 years after diagnosis	136	138	140	143	145	147
Initiate 3 years after diagnosis	134	136	138	140	143	145
Initiate 4 years after diagnosis	131	134	136	138	140	143
Total initiating CLL patients	1,100	1,118	1,136	1,153	1,170	1,187
Unfit for fludarabine (65%)	715	727	738	749	761	772
Total initiating ACAL patients (30%)	1	1	1	1	1	1
- VEN + OBI unsuitable (14%)	1	1	1	1	1	1
- VEN + OBI intolerant (16%)	1	1	1	1	1	1
Total ACAL treated patients (initiating and continuing)	1	1	2	2	2	2
Total ACAL scripts (██████/ year 96.8% adherence)	2	3	3	3	3	3
Estimated financial implications of acalabrutinib						
Total ACAL cost (\$██████ per script) less copayments	4	5	6	6	6	6
Estimated financial implications for other medicines						
Net saving for displaced OBI	7	7	7	7	7	7
Net saving for displaced CHL	7	7	7	7	7	7
Net saving for displaced ALLO	7	7	7	7	7	7
Net saving for displaced IBR	7	4	4	4	4	4
Net cost of additional IDEL	7	7	7	7	7	7
Net cost of additional RIT	7	7	7	7	7	7
Net saving to the PBS/RPBS	7	4	4	4	4	4
Net financial implications						
Net cost to the PBS/RPBS	7	7	4	5	5	5
Net saving to MBS	7	7	7	7	7	7
Net cost to Australian Government	7	7	4	5	5	5
July 2020 acalabrutinib submission						
Net cost to Australian Government	4	5	8	9	10	11

Source: Attachment 24_ACA_BIM_Section 4_Final' Excel workbook, Attachment 24 of the resubmission.

ACAL, acalabrutinib; ALLO, allopurinol; CHL, chlorambucil; CLL, chronic lymphocytic leukaemia; IBR, ibrutinib; IDEL, idelalisib; OBI, obinutuzumab; RIT, rituximab; VEN, venetoclax.

Blue highlighted cells indicate July 2020 estimates.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

⁶ \$30 million to < \$40 million

⁷ \$0 to < \$10 million

⁸ \$40 million to < \$50 million

⁹ \$60 million to < \$70 million

¹⁰ \$80 million to < \$90 million

¹¹ \$100 million to < \$200 million

- 6.62 The estimated net cost to the Australian Government was \$0 to < \$10 million in Year 1 of listing, increasing to \$20 million to < \$30 million in Year 6, an estimated net cost of \$100 million to < \$200 million over the first six years of listing. The July 2020 submission (based on a broader requested patient population) estimated a net cost to the Australian Government of \$10 million to < \$20 million in Year 1 of listing, increasing to \$100 million to < \$200 million in Year 6.
- 6.63 The estimated cost to the PBS/RPBS of listing acalabrutinib was considered uncertain due to the following reasons:
- The size of the eligible population was highly uncertain due to a lack of clarity regarding the definition of unsuitability for venetoclax + obinutuzumab treatment, and uncertainty regarding the proportion of patients who would discontinue venetoclax + obinutuzumab due to intolerance. The size of the population would remain highly uncertain if the restriction requirements were based on subjective criteria.
 - The utilisation estimates were based on the age-standardised incidence of CLL rather than the age-specific (crude) incidence, which may have resulted in underestimation of the incident CLL population.
 - It was unclear whether the assumed treatment duration for acalabrutinib, which was estimated from extrapolated time to treatment discontinuation data from the ELEVATE-TN trial, would reflect the time on treatment in clinical practice.
 - There is a high risk of use among patients who are suitable for treatment with venetoclax + obinutuzumab.
- 6.64 The estimated changes in use of other medicines were considered uncertain due to the following reasons:
- The approach used to estimate changes in ibrutinib and obinutuzumab script counts (based on a market share approach using PBS dispensing data) differed from the approach used to estimate the number of acalabrutinib and idelalisib scripts (epidemiological approach adjusted for trial-based utilisation). It was unclear whether the two approaches produced consistent results.
 - A proportion of patients treated with acalabrutinib in the first-line treatment setting may receive treatment with venetoclax + rituximab as a subsequent treatment, given the limited available options, and likely superiority of venetoclax + rituximab compared to idelalisib + rituximab.
 - The resubmission estimated the impact of RSAs for idelalisib and ibrutinib by assuming maximum treatment duration caps of 12 and 26 months, respectively. The assumed maximum treatment caps may not reflect the underlying RSA parameters.

Quality Use of Medicines

- 6.65 No quality use of medicines issues were raised in the resubmission, and no activities to support the quality use of medicines were proposed.

Financial Management – Risk Sharing Arrangements

- 6.66 The resubmission proposed an RSA in which the cost of acalabrutinib for each patient is capped at 48 months of treatment. The resubmission stated that the financial impact estimates, which incorporated time to treatment discontinuation data from the economic model (assuming a maximum treatment duration of 48 months), could be used to inform a cohort volume-based RSA with a total expenditure cap. The PBAC had previously considered that for assessments of cost-effectiveness to rely on RSA rebates, the PBAC would need to have a high level of confidence in the utilisation estimates underpinning the RSA (paragraph 10.56, ibrutinib, PSD, March 2018 PBAC meeting). This proposal seemingly would require such an RSA to continue indefinitely in order to ensure that expenditure beyond the initial 48 months (4 years) of listing is capped at this treatment duration. The ESC considered that this proposal was problematic given the lack of justification for the basis of the 48-month cap, and also that this was not a robust mechanism to achieve cost-effectiveness, especially given that the mean duration of treatment is likely to be much longer.
- 6.67 The pre-PBAC response noted the 48-month cap would only impact the last two years of the six-year estimates. To address this, the sponsor proposed a moving average in which the duration of subsidised treatment could be applied equally over all years within a Deed of Agreement, which would allow the improved cost-effectiveness benefits to be realised more rapidly. The Secretariat noted that agreements typically run for five years.
- 6.68 The pre-PBAC also noted that it would be acceptable to the sponsor to have an agreement specifically for first-line acalabrutinib only, or alternatively to be incorporated within a broader first-line CLL agreement that accounted for different prices and durations of treatment.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of acalabrutinib 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 and venetoclax + obinutuzumab, and for patients who permanently discontinue venetoclax + obinutuzumab due to intolerance.
- 7.2 The PBAC considered that the clinical evidence supported a benefit in this subgroup of CLL/SLL patients, but that the PBS restriction was subjective and patient numbers were unclear. The economic analysis was highly uncertain, and the incremental cost-effectiveness ratio was likely underestimated. A revised model, with a price reduction and reduced time horizon, would be required for PBAC decision making. Additionally, the sponsor would be required to provide further evidence that the proposed 48-month expenditure cap could be realised in practice, as this was critical to the resubmission's cost-effectiveness estimates and financial impact.

- 7.3 The PBAC noted that the consumer comments and sponsor hearing had described the convenience of an oral treatment as a benefit over alternative infusion-based regimens, highlighting the likelihood of improved access in rural and remote settings. The PBAC considered that the impact of the oral form was unclear as treated CLL/SLL patients all require monitoring, the intensity of which is determined not only by treatment type but also by treatment phase and patient factors. The PBAC also considered that the oral form presented a potential risk of inappropriate prescribing for non-symptomatic disease, when the evidence suggests most patients should be managed with a “watch and wait” approach. Overall, the PBAC considered it unclear what impact the oral form would have on treatment access and prescriber behaviour.
- 7.4 The PBAC considered that the requested restriction was difficult to interpret, but that even with refinement and further definition, the key clinical criteria around unsuitability for venetoclax + obinutuzumab treatment would remain subjective and it was unclear how the availability of acalabrutinib would affect prescribing choices.
- 7.5 The PBAC noted that the resubmission had proposed listing in a narrower population than the original submission, and that the PSCR had explained that the different durations of therapy between acalabrutinib and venetoclax + obinutuzumab would make it challenging to achieve cost-effectiveness for acalabrutinib in a comparison between these agents for the broader group of patients with previously untreated CLL/SLL (and unsuitable for a purine analogue). Hence, the sponsor had identified a narrower population in which there was a clinical need for alternative treatment options. The PBAC agreed with the ESC 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. Overall, the PBAC considered that there was scope for further refinement in the restrictions to improve clarity and remove duplication if the narrower listing was to be reconsidered.
- 7.6 The PBAC noted that the resubmission’s main proposed comparator was chlorambucil + obinutuzumab. The PBAC agreed that this was the main comparator for the proposed PBS population. Although it was noted this would not be the comparator for patients who discontinued venetoclax + obinutuzumab due to obinutuzumab intolerance, this was considered unlikely to affect the clinical or cost-effectiveness comparisons to a significant degree. Ibrutinib was not a main comparator for this resubmission given the proposed PBS population. As the requested PBS listing was for patients unsuitable for venetoclax + obinutuzumab, this combination was not a comparator in the resubmission, however, the PBAC recognised the issue that some patients/prescribers may prefer acalabrutinib as an oral therapy despite not being truly unsuitable for venetoclax + obinutuzumab (as raised by the evaluation, see paragraph 5.2). Based on the proposed restriction, the PBAC considered venetoclax + obinutuzumab to be a relevant comparator.
- 7.7 The PBAC recalled that it had previously considered the open-label phase 3 head-to-head randomised ELEVATE-TN trial at the July 2020 meeting, and it noted that the

resubmission had presented a later (September 2020) data cut with a median duration of follow up of 46.9 months. The PBAC noted the evaluation's concerns about applicability to the proposed PBS population. However, it agreed with the PSCR and the ESC that the trial would likely be applicable to the PBS population, commenting that the proposed PBS population could reasonably be considered a subgroup of ELEVATE-TN patients, and that the reasons for venetoclax + obinutuzumab unsuitability would not necessarily impact clinical response to therapy.

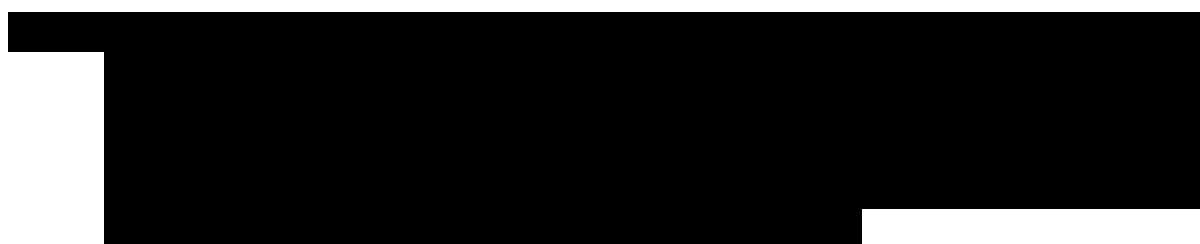
- 7.8 The PBAC recalled that, based on ELEVATE-TN, it had previously considered that a claim of superior comparative effectiveness between acalabrutinib and chlorambucil + obinutuzumab was reasonable, although the magnitude of the benefit had been uncertain at that time due to the immaturity of the data. The PBAC was more confident this claim was reasonable in relation to PFS, noting that the more mature data in the resubmission with follow-up over approximately four years showed consistency of effect. At the same time, it remained of the view that it would be inappropriate to model an overall survival gain in the economic evaluation as this data remained immature and there may not be a difference over the longer term given subsequent lines of effective therapy are available. It considered the overall superiority claim would be applicable to the narrower population proposed in the resubmission.
- 7.9 Similarly, the PBAC reiterated its previous opinion that ELEVATE-TN demonstrated likely superior safety of acalabrutinib over chlorambucil + obinutuzumab, noting that although acalabrutinib was associated with a higher incidence of serious adverse events, Grade ≥ 3 adverse events were lower, and the longer duration of treatment with acalabrutinib would be expected to have impacted the overall number of adverse events. It also considered that this claim applied to the narrower proposed PBS population.
- 7.10 In terms of the economic analysis, the PBAC noted the resubmission had revised its evaluation from using a Markov model to using a three-state partitioned survival model. 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. More importantly, the assumption applied in the acalabrutinib model arm did not reflect likely use in the PBS population, as many patients who were considered unsuitable for first-line venetoclax + obinutuzumab may use later-line venetoclax + rituximab, given it would provide reduced toxicity over idelalisib + rituximab (see paragraph 7.4, venetoclax, PSD, November 2018 PBAC meeting). The PBAC further noted the key model sensitivities identified by the ESC in paragraph 6.53 (time horizon, extrapolation of progression-free survival curve, the progressed state utility, and assumption of a treatment cap). The PBAC considered:

- 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.
- the extrapolated progression-free survival curve was subject to substantial uncertainty.
- the progressed disease state utility was consistent with the approach previously advised by the PBAC, although lower than that reported in the interim ELEVATE-TN trial analysis. The PBAC agreed with the ESC that it would have been informative to know when updated results will be available.
- 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.

7.11 Overall, the PBAC considered that the resulting incremental cost-effectiveness ratio was highly uncertain, and likely underestimated. Given the large uncertainty with respect to who will be considered unsuitable for venetoclax + obinutuzumab, the PBAC expected that a drug cost per patient more in line with this regimen would be required to achieve acceptable cost-effectiveness.

7.12 The PBAC agreed with the comments in paragraph 6.63 and 6.64 that the estimated cost to the PBS/RPBS of listing acalabrutinib and the estimated changes in use of other medicines were highly uncertain. The PBAC also noted the ESC's concerns about the proposed risk-sharing arrangement in paragraph 6.66, 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.

Committee-In-Confidence



End Committee-In-Confidence

7.14 The PBAC considered that a resubmission would need to, ideally, revise the restriction to include a broader population of patients to enable choice between the first-line treatment options. For either a broad or narrow listing, the PBAC noted the economic evaluation and financial forecasts would need to be revised based on the population proposed and to address the issues identified by ESC, and outlined in paragraph 7.10.

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

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.