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

1 Purpose of submission

1.1 The submission requested extending the March 2020 recommendation to also include a Section 85 (General Schedule), Authority Required listing for use as monotherapy, or in combination with obinutuzumab, for the treatment of:

- patients with untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) considered unsuitable for treatment with a purine analogue; or
- patients with untreated CLL or SLL who harbour a 17p deletion.

1.2 Listing for acalabrutinib monotherapy and acalabrutinib + obinutuzumab in the population unsuitable for treatment with a purine analogue was requested on the basis of a cost-effectiveness analysis versus chlorambucil + obinutuzumab. Listing for acalabrutinib monotherapy and acalabrutinib + obinutuzumab in the population of patients who harbour a 17p deletion was requested on the basis of a cost-minimisation analysis between acalabrutinib monotherapy and ibrutinib monotherapy.

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

Component	Description
Population	Patients with previously untreated CLL or SLL considered unsuitable for treatment with a purine analogue; OR Patients with previously untreated CLL or SLL who harbour a 17p deletion.
Intervention	- Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity - Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity + IV obinutuzumab eight infusions of 1,000 mg over six cycles
Comparator	Primary comparator: Oral chlorambucil for 6 cycles + IV obinutuzumab 8 infusions of 1,000 mg over 6 cycles Supplementary near-market comparator: Oral venetoclax 5-week dose titration followed by 400 mg daily for 12 cycles + IV obinutuzumab 8 infusions of 1,000 mg over 6 cycles Comparator for patients with 17p deletion: Oral ibrutinib 420 mg once daily until disease progression or unacceptable toxicity
Outcomes	PFS, ORR, OS, safety.
Clinical claim	In patients with previously untreated CLL considered unsuitable for treatment with a purine analogue: - Acalabrutinib + obinutuzumab is superior in terms of efficacy, and no worse in terms of safety compared to chlorambucil + obinutuzumab. - Acalabrutinib monotherapy is superior in terms of efficacy and safety compared to chlorambucil plus obinutuzumab. - Acalabrutinib + obinutuzumab is non-inferior in terms of PFS and OS but has a higher ORR compared to venetoclax + obinutuzumab, and is non-inferior in terms of safety compared to venetoclax + obinutuzumab. - Acalabrutinib monotherapy is non-inferior in terms of efficacy, and superior in terms of safety compared to venetoclax + obinutuzumab. In patients with previously untreated CLL with 17p deletion considered unsuitable for treatment with a purine analogue: - Acalabrutinib monotherapy is non-inferior in terms of efficacy, and superior in terms of safety compared to ibrutinib monotherapy.

CLL = chronic lymphocytic leukaemia; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression free survival; SLL = small lymphocytic lymphoma.
Source: Table 1.1, p.5 of the submission; Section 1.17, p.23 of 'Appendix 1 Near Market Comparison' document.

2 Background

Registration status

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

2.2 The submission noted that a co-dependent submission to MSAC has been lodged requesting the addition of acalabrutinib to Item 73343, in order to allow 17p deletion testing in patients with relapsed/refractory (RR) CLL/SLL for the purpose of assessing eligibility for acalabrutinib treatment (MSAC Item 1607). The submission also noted that a co-dependent submission to MSAC for ibrutinib requesting expansion of MBS item 73343 to include previously untreated patients (MSAC application 1560) was supported by MSAC.

2.3 The submission stated that in the case that MSAC Application 1607 is not supported or the ibrutinib recommendation does not progress to listing, a minor submission would be lodged to MSAC requesting changes to MBS Item 73343 to allow 17p

deletion testing in previously untreated patients for the purpose of assessing eligibility for acalabrutinib treatment.

Previous PBAC consideration

2.4 Acalabrutinib has not previously been considered by PBAC in patients with untreated CLL/SLL. A submission for acalabrutinib monotherapy for the treatment of RR CLL/SLL was recommended for listing at the March 2020 PBAC meeting.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ACALABRUTINIB Capsules 100mg, 56	1	5	$9,279.12 published price $[redacted] effective price	Calquence® AstraZeneca Australia Pty Ltd

Category/Program:	GENERAL – General Schedule (Code GE)
PBS indication:	Chronic lymphocytic leukaemia or small lymphocytic lymphoma in patients considered unsuitable for treatment with a purine analogue
Treatment phase:	Initial and continuing treatment
Restriction:	Authority Required – Telephone (initial treatment)/Streamlined (continuing treatment)
Clinical criteria (initial):	The condition must be previously untreated, AND Patient must be considered unsuitable for treatment with a purine analogue AND Patient must have an ECOG performance status of ≤ 2
Clinical criteria (continuing):	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
Prescriber criteria:	A patient is considered unsuitable for treatment with a purine analogue as demonstrated by at least one of the following: a) Age is 65 years or older; b) Age is older than 18 years but younger than 65 years and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater), or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy. c) 17p(del)

3.1 The submission proposed a special pricing arrangement (SPA), with a [redacted]% rebate on the proposed published price.

3.2 The proposed restriction is narrower than the TGA indication, which does not require patients to be unsuitable for treatment with a purine analogue and therefore does not restrict treatment based on age, presence of 17p deletion, Cumulative Illness Rating Scale (CIRS) score or renal function. The proposed clinical criteria are generally consistent with the eligibility criteria for the ELEVATE-TN trial. However, the proposed restriction specifies a CIRS score of ≥ 6, whereas the ELEVATE-TN trial recruited patients with a CIRS score of > 6. Additionally, while patients with 17p deletion were

not excluded from the ELEVATE-TN trial, the presence of 17p deletion was not a specific inclusion criterion.

3.3 The proposed restriction includes all patients over the age of 65 years, patients less than 65 years with a CIRS score ≥ 6 or creatinine clearance < 70 mL/min, or patients with 17p deletion. This differs from the clinical criteria included in the obinutuzumab restriction, which specify a CIRS score > 6 or a creatinine clearance of < 70 mL/min for all patients (regardless of age). Additionally, the proposed restriction specifies an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (consistent with the ELEVATE-TN trial) whereas the obinutuzumab restriction does not include an ECOG performance status requirement, and the proposed restriction does not specify a minimum creatinine clearance, whereas the obinutuzumab restriction specifies a creatinine clearance of at least 30 mL/min.

3.4 The proposed restriction does not specify that acalabrutinib can be used as monotherapy or in combination with obinutuzumab. It does not preclude the use of acalabrutinib in combination with treatments other than obinutuzumab.

3.5 The proposed restriction differs from the recommended ibrutinib restriction, which is limited to patients with 17p deletion. The proposed restriction does not specify a method for the assessment of 17p deletion whereas the recommended restriction for ibrutinib specifies that patients must have evidence of one or more 17p chromosomal deletions as demonstrated by fluorescence in situ hybridisation. The recommended restriction for ibrutinib states that a patient may only qualify for PBS-subsidised initial treatment under the untreated CLL/SLL or RR CLL/SLL once in a lifetime. In addition, the proposed restriction does not specify whether treatment in the 17p deletion population should be restricted to acalabrutinib monotherapy. The submission provided no clinical or economic evidence to support the use of acalabrutinib + obinutuzumab in this population.

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. The submission noted that the results of a web-based survey of 1,482 CLL patients assessing the impact of CLL on the quality of life of patients indicated that CLL-related symptoms and comorbidities markedly reduced quality of life, with fatigue being the most recognised disease-related symptom (Shanafelt et al., 2007).

4.2 CLL is more common in men than women (65% versus 35%), with a mean age at diagnosis in Australia of 70 years (males 68.8 years, females 71.2 years). The five-year relative survival rate in Australia in 2011-2015 was 82.8% (AIHW, 2019). CLL and SLL

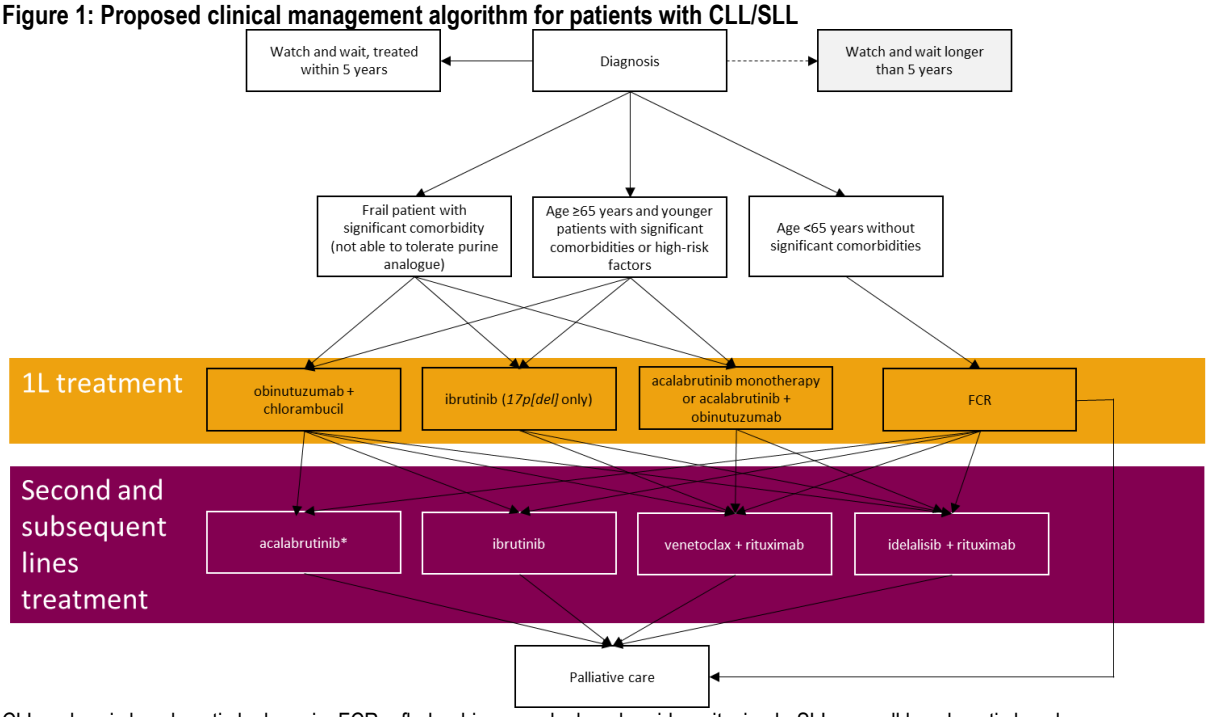
are considered to be different manifestations of the same disease. In CLL, abnormal lymphocytes are predominantly found in blood, bone marrow and lymphoid tissue, whereas in SLL, abnormal lymphocytes are predominantly located in lymph nodes, bone marrow and other lymphoid tissue.

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 β2 microglobulin), and patient characteristics (male sex, older age, worse ECOG performance score). Deletion of the short arm of chromosome 17 (17p deletion) is found in 5-8% of chemotherapy-naïve patients, and is associated with resistance to genotoxic chemotherapies, including conventional chemoimmunotherapy regimens (Hallek, 2015).

4.4 CLL/SLL is generally a slowly progressing cancer, with many patients managed with a 'watch and wait' approach until symptoms develop. The choice of therapy depends on a number of factors, including age, fitness, comorbidities, and the presence of prognostic genetic mutations.

4.5 Figure 1 below presents the proposed clinical management algorithm presented in the submission. The algorithm positions acalabrutinib monotherapy and acalabrutinib + obinutuzumab as first-line options 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. The proposed algorithm does not include criteria to guide selection of treatment with acalabrutinib + obinutuzumab versus acalabrutinib monotherapy. The submission claimed that 80% of patients would be treated with acalabrutinib monotherapy due to the improved safety profile of acalabrutinib monotherapy compared to acalabrutinib + obinutuzumab. The ESC considered that the majority of patients without the 17p deletion would receive treatment with acalabrutinib monotherapy as the proposed restriction required patients unfit for fludarabine-based chemotherapy to be aged 65 years or older or to have comorbidities. The ESC considered that for patients with the 17p deletion, the majority would receive combination therapy of acalabrutinib + obinutuzumab as, per the proposed restriction, these patients are likely to be younger and fitter, and they require a greater depth of response.

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



CLL = chronic lymphocytic leukaemia; FCR = fludarabine + cyclophosphamide + rituximab; SLL = small lymphocytic lymphoma
Source: Figure 1.9, p.24 of the submission.
* Assumes a positive PBAC recommendation at the March 2020 meeting.

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

5 Comparator

5.1 The submission nominated chlorambucil + obinutuzumab as the main comparator for acalabrutinib ± obinutuzumab. The main arguments provided in support of this nomination were:

- Obinutuzumab is listed on the PBS for use in combination with chlorambucil in patients with previously untreated CLL considered unsuitable for treatment with fludarabine-based chemo-immunotherapy, and who have a CIRS score > 6 or a creatine clearance between 30 mL/min and 70 mL/min.
- Chlorambucil + obinutuzumab is the therapy most likely to be replaced by the listing of acalabrutinib ± obinutuzumab, based on an analysis of PBS data conducted by the sponsor.
- Chlorambucil + obinutuzumab was previously accepted as a comparator in the PBAC submissions for ibrutinib monotherapy in patients with untreated CLL that are unsuitable for treatment with a purine analogue.

The ESC considered chlorambucil + obinutuzumab to be an appropriate comparator.

5.2 The submission nominated ibrutinib monotherapy as a secondary comparator for patients with 17p deletion. Ibrutinib monotherapy was recommended at the November 2019 PBAC meeting for the treatment of previously untreated patients with 17p deletion. However, the submission argued that ibrutinib was a relevant

comparator for acalabrutinib monotherapy only. This may not be reasonable given that the requested listing is for acalabrutinib monotherapy and acalabrutinib + obinutuzumab, and clinical guidelines include both acalabrutinib monotherapy and acalabrutinib + obinutuzumab as preferred first-line treatments for patients with 17p deletion. In patients with 17p deletion the ESC considered that ibrutinib monotherapy should have been considered as a comparator for acalabrutinib + obinutuzumab as these patients are likely to be treated with combination therapy. The pre-PBAC response agreed that the well-known poor prognosis of 17p deletion patients means they would be more likely to be considered for a more aggressive treatment regimen, such as acalabrutinib + obinutuzumab.

5.3 The submission nominated venetoclax + obinutuzumab as a near market comparator. The ESC considered that this was reasonable. A submission for venetoclax + obinutuzumab for the first-line treatment of patients with CLL who have coexisting conditions and are unsuitable for fludarabine based chemotherapy was rejected by the PBAC at the March 2020 meeting. A minor resubmission for venetoclax + obinutuzumab in the first-line setting was also considered by the PBAC at the July 2020 meeting.

5.4 The submission noted that chlorambucil may also be used in combination with rituximab in the first-line treatment setting, but argued that the results of the CLL-11 trial (chlorambucil + obinutuzumab versus chlorambucil + rituximab) demonstrated that chlorambucil + obinutuzumab has superior efficacy compared to chlorambucil + rituximab. The PBAC previously considered that chlorambucil + obinutuzumab provides, for some patients, a significant improvement in efficacy over chlorambucil + rituximab, and chlorambucil monotherapy (paragraph 7.2, obinutuzumab, Public Summary Document, March 2015 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (13) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with acalabrutinib including the improved quality of life associated with a less toxic first-line treatment option for older, less fit patients.

6.3 The PBAC noted the advice received from the Leukaemia Foundation, Lymphoma Australia and Rare Cancers Australia clarifying the likely use of acalabrutinib in clinical practice. The PBAC specifically noted the advice that acalabrutinib in the first-line

setting would meet a high unmet clinical need and provide a treatment option for elderly, chemotherapy contraindicated patients.

Clinical trials

6.4 The submission was based on the following comparisons of acalabrutinib ± obinutuzumab and the nominated comparators:

- A head-to-head comparison of acalabrutinib monotherapy, acalabrutinib + obinutuzumab, and chlorambucil + obinutuzumab (ELEVATE-TN);
- A naïve comparison and an unanchored matching adjusted indirect comparison (MAIC) of acalabrutinib + obinutuzumab (ELEVATE-TN) versus venetoclax + obinutuzumab (CLL-14);
- A naïve comparison and an unanchored MAIC of acalabrutinib monotherapy (ELEVATE-TN) versus venetoclax + obinutuzumab (CLL-14).
- A naïve comparison and an unanchored MAIC of acalabrutinib monotherapy (ELEVATE-TN) versus ibrutinib monotherapy (RESONATE-2) based on the assumption that the results of the comparison based on the full trial populations could be used as a proxy for patients with 17p deletion.

The submission did not include a comparison of acalabrutinib + obinutuzumab versus ibrutinib monotherapy in patients with 17p deletion. The ESC considered that this was not reasonable given that the requested listing is for both acalabrutinib monotherapy and acalabrutinib + obinutuzumab and as the majority of 17p deletion patients would likely receive acalabrutinib + obinutuzumab.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Acalabrutinib ± obinutuzumab trials		
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.	Clinical Study Report, 16 August 2019.
Ibrutinib trials		
RESONATE-2 NCT01722487	Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukaemia.	*New England Journal of Medicine* 2015; 373(25): 2425-37.
RESONATE-2 Extension NCT01724346	Barr PM, Robak T, Owen C, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukaemia: extended phase 3 results from RESONATE-2.	*Haematologica* 2018; 103(9): 1502-1510.
Venetoclax + obinutuzumab trials		
CLL-14 NCT02242942	Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions.	*New England Journal of Medicine* 2019; 380(23): 2225-2236.

Source: Table 2.3, p.35 of the submission; Table A1.3, pp5-6 of 'Appendix 1 Near Market Comparators' of the submission.
References relating to conference abstracts omitted.

6.6 The submission excluded two identified trials which the ESC considered may have been informative:

- the ALLIANCE trial on the basis of 'wrong comparator'. The ALLIANCE trial was a phase 3, randomised trial of ibrutinib, ibrutinib plus rituximab, or bendamustine + rituximab in patients aged ≥ 65 years who had untreated intermediate or high-risk Rai-stage CLL. Given that the submission relied upon a naïve comparison and an unanchored MAIC of acalabrutinib monotherapy and ibrutinib monotherapy using the RESONATE-2 trial (due to the absence of a common comparator), this exclusion may not be reasonable; and
- the iLLUMINATE trial on the basis of 'wrong intervention'. The iLLUMINATE trial was a Phase 3 randomised trial comparing ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab in patients considered unsuitable for fludarabine based chemoimmunotherapy (aged ≥ 65 years or aged < 65 years with a least one of: CIRS score > 6, creatinine clearance < 70 mL/min, presence of 17p deletion, presence of TP53 mutation). A comparison of acalabrutinib + obinutuzumab (ELEVATE-TN) versus ibrutinib + obinutuzumab (iLLUMINATE) may have been informative given that the trials share a common comparator (chlorambucil + obinutuzumab), had similar eligibility criteria, and clinical evidence from the iLLUMINATE trial formed the basis for the positive PBAC recommendation of ibrutinib monotherapy for previously untreated patients with 17p deletion.

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

Table 3: Key features of the included evidence

Trial	N	Design/duration of follow-up	Risk of bias	Patient population	Outcomes
Acalabrutinib + obinutuzumab vs. acalabrutinib monotherapy vs. chlorambucil + obinutuzumab					
ELEVATE-TN	535	Phase 3, R, OL trial; Median duration of follow-up 28 months	Unclear	• ≥ 65 years; • 18-65 years with a 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.	• PFS • ORR • OS • TTNT • AEs • HRQOL (FACIT-Fatigue, EORTC QLQ-C30, EQ-5D-3L).
Ibrutinib vs. chlorambucil					
RESONATE-2	269	Phase 3, R, OL trial; Median duration of follow-up 29 months	Unclear	• > 65 years (patients 65-70 years were required to have ≥ 1 of: o CrCl < 70 mL/min o platelet count < 100,000/μL o haemoglobin < 10 g/dL o autoimmune cytopenia o ECOG score of 1-2 • Active CLL/SLL disease requiring treatment • No prior CLL/SLL treatment • ECOG score ≤ 2 • Excluded patients with 17p deletion.	• PFS • ORR • OS • Rate of MRD-negative CR • AEs • HRQOL (EORTC QLQ-C30, EQ-5D-5L).
Venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab					
CLL-14	432	Phase 3, R, OL trial; Median duration of follow-up 28 months	Unclear	• ≥ 18 years; • CIRS score > 6 or CrCl < 70 mL/min; • CLL disease requiring treatment • Previously untreated CLL	• PFS • ORR • OS • TTNT • MRD response rate • Duration of response • Event-free survival • AEs • HRQOL (MDASI, EORTC QLQ-C30, EQ-5D-5L).

AE = adverse event; CD = cluster of differentiation; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CR = complete response; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQoL 5-Dimension; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; HRQOL = health-related quality of life; MDASI = MD Anderson Symptom Inventory; MRD = minimal residual disease; OL = open-label; ORR = overall response rate; OS = overall survival; PFS = progression free survival; QLQ = quality of life questionnaire; R = randomised; SLL = small lymphocytic lymphoma; TTNT = time to next treatment

Source: Table S1, pp2-4 and pp42-46 of the ELEVATE-TN interim clinical study report; pp44-49 of the CLL-14 trial protocol (Fischer et al., 2019); pp10-15 of the RESONATE-2 trial protocol (Burger et al., 2015).

6.8 The ELEVATE-TN, RESONATE-2 and CLL-14 trials had an unclear risk of bias. As the trials were open label, investigators, patients, and study personnel were not blinded to treatment allocation, which may have influenced the treatment of patients in the trial. Assessments made by study investigators (who were not blinded to treatment allocation) were at high risk of bias. Each trial included blinded assessments by an independent review committee, which had a lower risk of assessment bias.

6.9 The PBAC noted that there were major differences between the included trials in eligibility criteria, including:

- The ELEVATE-TN trial recruited patients aged at least 65 years as well as patients aged less than 65 years with a creatinine clearance of 30 to 69 mL/min or a CIRS score > 6.
- The RESONATE-2 trial excluded patients under 65 years of age. Patients aged 65 to 70 years were required to meet at least one of the following criteria: creatinine clearance < 70 mL/min, platelet count < 100,000/µL, haemoglobin < 10 g/dL, clinically apparent autoimmune cytopenia, or an ECOG score of 1-2. Patients with 17p deletion were excluded.
- The CLL-14 trial recruited patients aged at least 18 years who had a creatinine clearance < 70 mL/min or a CIRS score > 6.

6.10 The trials included patients with broadly similar median age, proportion of males, and median time since diagnosis. However, a lack of reporting for some patient characteristics in the RESONATE-2 and CLL-14 trials (race, geographic region, disease stage, tumour lysis syndrome risk, bulky disease strata, creatinine clearance strata) limited the ability to compare baseline characteristics across trials.

6.11 The proportion of patients with a CIRS score > 6 was substantially higher in the CLL-14 trial (86% and 82% in the venetoclax + obinutuzumab and chlorambucil + obinutuzumab arms, respectively) compared to the RESONATE-2 trial (31% in the ibrutinib arm and 33% in the chlorambucil arm). The proportion of patients with a CIRS score > 6 in the ELEVATE-TN trial was only reported for patients aged < 65 years (17% in the acalabrutinib + obinutuzumab arm, 12% in the acalabrutinib monotherapy arm, and 9% in the chlorambucil + obinutuzumab arm). The proportion of patients with 17p deletion was similar for the ELEVATE-TN (8.9 to 9.5%) and the CLL-14 trials (7.3% to 8.5%). The RESONATE-2 trial excluded patients with 17p deletion.

6.12 There were differences in the chlorambucil dosing between the trials. In the ELEVATE-TN and CLL-14 trials, patients in the comparator arms received treatment with chlorambucil in combination with six cycles of obinutuzumab. In the RESONATE-2 trial, patients in the comparator arm received treatment with chlorambucil only. The chlorambucil dose was 0.5 mg/kg in ELEVATE-TN and CLL-14. In RESONATE-2, the initial dose was 0.5 mg/kg, but the dose could be increased in increments of 0.1 mg/kg each cycle to a maximum of 0.8 mg/kg if well tolerated.

6.13 There were differences between the trials in the duration of treatments. In the CLL-14 trial, treatment with venetoclax was based on a fixed treatment duration of 12 cycles (48 weeks). Treatment with acalabrutinib and ibrutinib was ongoing until disease progression in ELEVATE-TN and RESONATE-2. In ELEVATE-TN, patients received treatment with chlorambucil for up to 6 cycles (24 weeks), whereas patients in RESONATE-2 and CLL-14 received up to 12 cycles of chlorambucil (48 weeks).

6.14 In the ELEVATE-TN trial, patients in the obinutuzumab + chlorambucil arm who had independent review committee-confirmed disease progression were eligible to

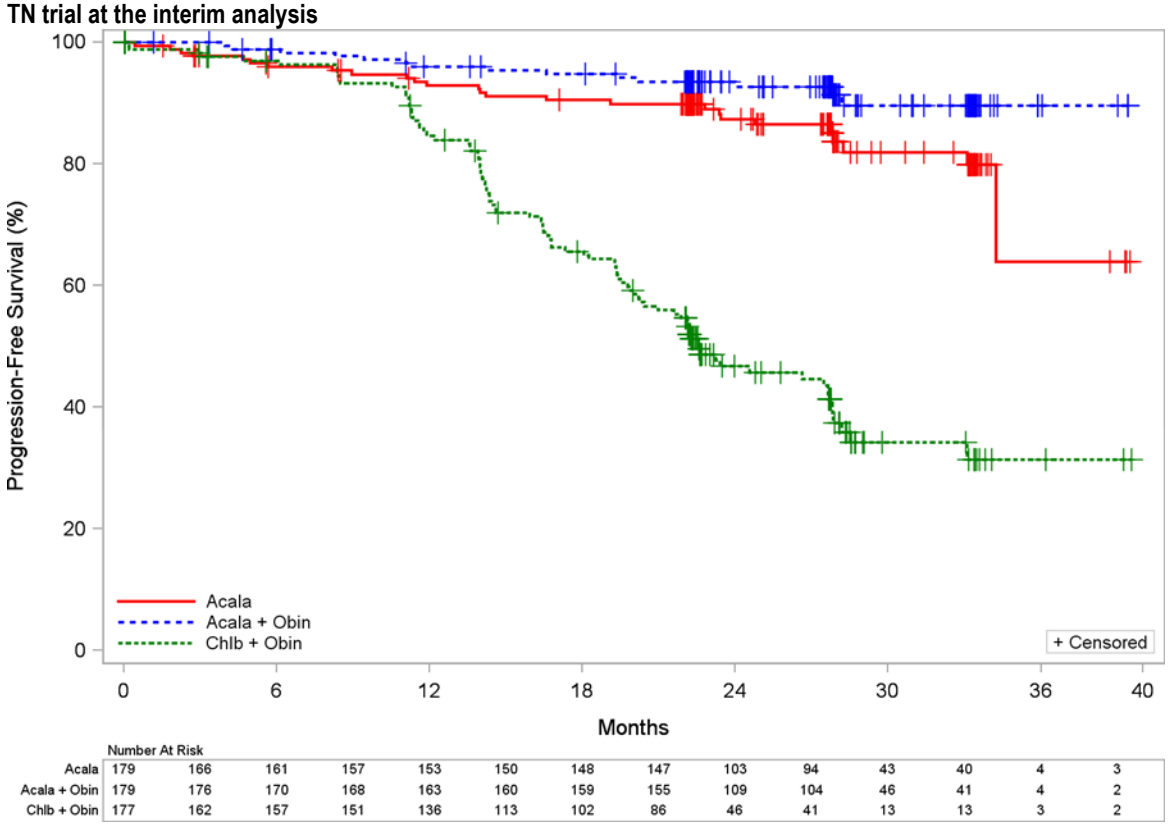
receive crossover treatment with acalabrutinib monotherapy. At the interim analysis, 45/177 (25.4%) patients had crossed over from the chlorambucil + obinutuzumab treatment arm to receive acalabrutinib monotherapy, with 41/45 (91.1%) remaining on acalabrutinib monotherapy. Crossover to receive ibrutinib was permitted in the RESONATE-2 trial. Crossover to receive venetoclax was not permitted in CLL-14.

6.15 The submission argued that it is difficult to define a minimal clinically important difference (MCID) for efficacy outcomes (i.e. PFS, OS, ORR, TTNT), as there is no generally accepted level of clinically important difference for efficacy outcome measures for CLL patients. The submission proposed an MCID of approximately 18 months for progression free survival, based on the sample size calculation for the ELEVATE-TN trial, which was calculated according to a target hazard ratio of 0.6 for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab (equating to an approximately 18-month absolute increase in median progression free survival). No non-inferiority margin was proposed in the submission.

Comparative effectiveness

6.16 Figure 2 presents the Kaplan-Meier plot of independent review committee assessed-progression free survival for the ELEVATE-TN trial at the interim analysis (median follow-up = 28 months).

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



Acala = acalabrutinib; Chlb = chlorambucil; Obin = obinutuzumab.
Source: Figure 2.3, p.66 of the submission.

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

Table 4: Progression free survival results for the ELEVATE-TN trial at the 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			
Earliest event total, n (%) - Progression, n - Death, n	14 (7.8%) 9 5	26 (14.5%) 20 6	93 (52.5%) 82 11
Median PFS, months (95% CI)	Not reached (NE)	Not reached (34.2, NE)	22.6 (20.2, 27.6)
Stratified HR vs CHL + OBI (95% CI)	**0.10 (0.06, 0.17)**	**0.20 (0.13, 0.30)**	-
KM estimate of PFS - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI) - 24 months, % (95% CI) - 30 months, % (95% CI) - 36 months, % (95% CI)	 98.9% (95.5, 99.7) 95.9% (91.7, 98.0) 94.8% (90.2, 97.2) 92.7% (87.4, 95.8) 89.6% (82.0, 94.1) 89.6% (82.0, 94.1)	 95.9% (91.6, 98.0) 92.9% (87.8, 95.9) 90.5% (84.9, 94.1) 87.3% (80.9, 91.7) 81.9% (73.3, 88.0) 63.9% (29.4, 84.9)	 97.0% (92.9, 98.7) 84.6% (78.0, 89.3) 65.6% (57.7, 72.4) 46.7% (38.5, 54.6) 34.2% (25.3, 43.2) 31.3% (21.8, 41.3)
Investigator-assessed			
Earliest event total, n (%) - Progression, n - Death, n	15 (8.4%) 9 6	19 (10.6%) 12 7	86 (48.6%) 75 11
Median PFS, months (95% CI)	Not reached (NE)	Not reached (NE)	27.8 (22.6, 28.8)
Stratified HR vs CHL + OBI (95% CI)	**0.12 (0.07, 0.21)**	**0.16 (0.10, 0.27)**	-
KM estimate of PFS - 6 months, % (95% CI) - 12 months, % (95% CI) - 18 months, % (95% CI) - 24 months, % (95% CI) - 30 months, % (95% CI) - 36 months, % (95% CI)	 98.3% (94.8, 99.5) 95.4% (91.1, 97.7) 94.3% (89.6, 96.9) 91.9% (86.7, 95.1) 90.9% (85.3, 94.5) 90.9% (85.3, 94.5)	 97.1% (93.2, 98.8) 94.7% (90.1, 97.2) 92.9% (87.8, 95.9) 90.4% (84.9, 94.0) 87.6% (81.0, 92.1) 87.6% (81.0, 92.1)	 95.2% (90.7, 97.6) 85.5% (79.1, 90.0) 68.8% (61.0, 75.3) 54.7% (46.7, 62.0) 39.9% (30.6, 49.1) 36.9% (26.6, 47.1)

ACAL = acalabrutinib; CHL = chlorambucil; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; OBI = obinutuzumab; PFS = progression free survival.
Source: Table 2.20, p.65 of the submission; Table 14, pp97-98; Table 22, p.121 of the ELEVATE-TN interim clinical study report.

6.18 At a median duration of follow-up of 28 months, independent review committee-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 22.6 months for chlorambucil + obinutuzumab; HR = 0.10 [95% CI: 0.06, 0.17] for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab; HR = 0.20 [95% CI: 0.13, 0.30] for acalabrutinib monotherapy versus chlorambucil + obinutuzumab). The ESC noted that the data were immature as median progression free survival had not been reached for either acalabrutinib arm.

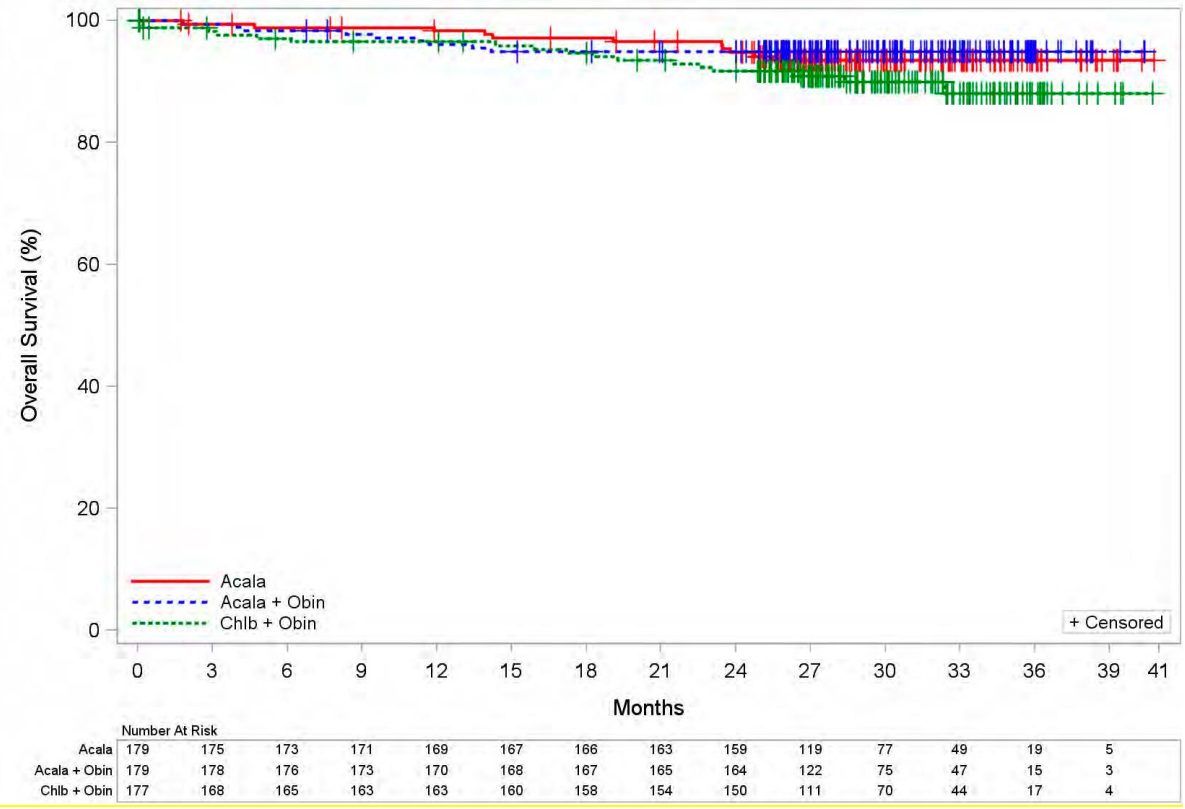
6.19 Treatment with acalabrutinib + obinutuzumab was associated with a small numerical improvement in progression free survival compared to acalabrutinib monotherapy. However, statistical testing for a difference between the acalabrutinib +

obinutuzumab and acalabrutinib monotherapy arms was not included in the submission. The Pre-Sub-Committee Response (PSCR) provided results from a post-hoc analysis (Sharman, 2020) which reported that acalabrutinib + obinutuzumab was associated with a greater independent review committee-assessed progression free survival compared to acalabrutinib monotherapy (HR = 0.49 [95% CI: 0.26, 0.95]). The difference for combination versus monotherapy treatment was smaller based on investigator-assessed progression free survival (Table 4).

6.20 Among patients with 17p deletion, independent review committee-assessed progression free survival was statistically significantly longer in the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms compared to the chlorambucil + obinutuzumab arm (HR = 0.13 [95% CI: 0.04, 0.46] for acalabrutinib + obinutuzumab; HR = 0.20 [95% CI: 0.06, 0.64] for acalabrutinib monotherapy). The results based on patients with 17p deletion were consistent with the results for the full trial population. However, the results should be interpreted with caution due to the small number of patients with 17p deletion included in the trial (approximately 11% of the trial population).

6.21 Figure 3 presents the Kaplan-Meier plot of overall survival for the ELEVATE-TN trial at the interim analysis.

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



Acala = acalabrutinib; Chlb = chlorambucil; Obin = obinutuzumab.
Source: Figure 14.2.4.1, p.195 of the 'ELEVATE-csr-section-tables-listings-figures' pdf document.

6.22 Table 5 presents the results for overall survival for the ELEVATE-TN trial at the interim analysis (median follow-up = 28 months).

Table 5: Overall survival results for the ELEVATE-TN trial at the 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)
Death, n (%)	9 (5.0%)	11 (6.1%)	17 (9.6%)
Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	Not reached (NE)
Stratified HR vs CHL + OBI (95% CI)	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	-
KM estimate of OS			
- 6 months, % (95% CI)	98.3% (94.9, 99.5)	98.9% (95.5, 99.7)	97.1% (93.2, 98.8)
- 12 months, % (95% CI)	96.1% (91.9, 98.1)	98.3% (94.8, 99.4)	96.5% (92.4, 98.4)
- 18 months, % (95% CI)	94.9% (90.5, 97.3)	97.1% (93.2, 98.8)	94.7% (90.1, 97.2)
- 24 months, % (95% CI)	94.9% (90.5, 97.3)	94.7% (90.2, 97.2)	91.7% (86.3, 95.0)
- 30 months, % (95% CI)	94.9% (90.5, 97.3)	93.5% (88.6, 96.3)	89.9% (83.9, 93.7)
- 36 months, % (95% CI)	94.9% (90.5, 97.3)	93.5% (88.6, 96.3)	88.1% (80.7, 92.8)

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

Source: Table 2.24, pp69-70 of the submission; Table 22, p.121 of the ELEVATE-TN interim clinical study report.

6.23 At a median duration of follow-up of 28 months, median overall survival was not reached for acalabrutinib + obinutuzumab, acalabrutinib monotherapy or chlorambucil + obinutuzumab. There was no statistically significant difference for acalabrutinib + obinutuzumab, or acalabrutinib monotherapy compared to chlorambucil + obinutuzumab. Low numbers of events in each arm indicate that the overall survival results are immature. Statistical testing for a difference between the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms was not included in the submission. Overall survival results were impacted by patient crossover from the chlorambucil + obinutuzumab arm to receive treatment with acalabrutinib monotherapy. At the interim analysis, 45 patients (25.4%) in the chlorambucil + obinutuzumab arm who had experienced disease progression had crossed over to receive acalabrutinib. Overall survival may not be expected to be different due to downstream effective treatments and the older mean age at diagnosis (70 years), i.e. patients may die of other causes.

6.24 Table 6 presents the results for independent review committee and investigator-assessed overall response for the ELEVATE-TN trial at the interim analysis.

Table 6: Overall response results for the ELEVATE-TN trial at the 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			
ORR (CR + CRi + nPR + PR), n (%)	168 (93.9%)	153 (85.5%)	139 (78.5%)
Difference versus CHL + OBI (95% CI)	15.3 (8.3, 22.3)	6.9 (-1.0, 14.9)	-
Investigator-assessed			
ORR (CR + CRi + nPR + PR), n (%)	172 (96.1%)	160 (89.4%)	146 (82.5%)
Difference versus CHL + OBI (95% CI)	13.6 (7.3, 19.9)	6.9 (-0.3, 14.1)	-

ACAL = acalabrutinib; CHL = chlorambucil; CI = confidence interval; CR = complete response; Cri = complete response with incomplete bone marrow recovery; nPR = nodular partial response; OBI = obinutuzumab; ORR = overall response rate; PR = partial response.
Source: Table 2.22, pp67-68 of the submission; Table 18, p.110 of the ELEVATE-TN interim clinical study report.

6.25 Based on the independent review committee-assessed outcomes, 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]). Statistical testing for a difference between the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms was not included in the submission.

6.26 Table 7 presents the results for time to next anti-CLL treatment for the ELEVATE-TN trial at the interim analysis. A Kaplan-Meier plot of time to next treatment was not included in the submission.

Table 7: Time to next treatment results for the ELEVATE-TN trial at the 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 (%) - Death, n (%) - Crossover treatment, n (%) - Subsequent anti-cancer therapy, n (%)	13 (7.3%) 8 (4.5%) 0 5 (2.8%)	21 (11.7%) 10 (5.6%) 0 11 (6.1%)	70 (39.5%) 15 (8.5%) 45 (25.4%) 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) - 12 months, % (95% CI) - 18 months, % (95% CI) - 24 months, % (95% CI) - 30 months, % (95% CI) - 36 months, % (95% CI)	 97.8% (94.2, 99.2) 94.9% (90.5, 97.3) 93.2% (88.4, 96.1) 93.2% (88.4, 96.1) 93.2% (88.4, 96.1) 90.0% (80.0, 95.2)	 96.6% (92.6, 98.5) 94.3% (89.7, 96.9) 92.6% (87.5, 95.6) 90.2% (84.7, 93.8) 87.9% (81.8, 92.1) 86.3% (79.2, 91.1)	 95.3% (90.9, 97.6) 92.9% (87.9, 95.9) 78.5% (71.5, 84.0) 67.0% (59.2, 73.6) 55.5% (46.5, 63.5) 50.2% (40.3, 59.3)

ACAL = acalabrutinib; CHL = chlorambucil; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; OBI = obinutuzumab; TTNT = time to next treatment.
Source: Table 2.23, p.68 of the submission; Table 20, p118 of the ELEVATE-TN interim clinical study report.

6.27 At a median duration of follow-up of 28 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. 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.

6.28 Patients across all three arms showed improvements in the FACIT-Fatigue Global Fatigue Score that exceeded the nominated clinically important difference of three points. There were no statistically significant differences between groups for any of the FACIT-Fatigue domains.

6.29 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.

6.30 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.

Matching adjusted indirect comparisons (MAICs)

6.31 The submission presented the results of three unanchored MAICs:

- A comparison of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab based on individual patient data from the ELEVATE-TN trial and published data for the CLL-14 trial;
- A comparison of acalabrutinib monotherapy versus venetoclax + obinutuzumab based on individual patient data from the ELEVATE-TN trial and published data for the CLL-14 trial;
- A comparison of acalabrutinib monotherapy versus ibrutinib monotherapy based on individual patient data from the ELEVATE-TN trial and published data for the RESONATE-2 trial. The RESONATE-2 trial excluded patients with 17p deletion and only 8.9% (16/179) of patients in the acalabrutinib monotherapy arm of the ELEVATE-TN trial had 17p deletion. The submission argued that the results of the comparison based on the full trial populations could be used as a proxy for patients with 17p deletion. The ESC considered that the outcomes of BTK inhibitors in patients with 17p deletion would likely be similar to the outcomes in patients without 17p deletion. The PBAC agreed that the outcomes would likely be similar, but considered that a comparison of results for patients with and without 17p deletion would be informative.

6.32 Summary results of the MAICs are presented in Table 8.

Table 8: Results of the MAICs versus ibrutinib monotherapy and venetoclax + obinutuzumab

	ACAL+OBI vs VEN+OBI	ACAL vs VEN+OBI	ACAL vs IBR
Patients in acalabrutinib arm in ELEVATE-TN	179	179	179
Acalabrutinib patients included in MAIC prior to matching[1]	[redacted]	[redacted]	136
Acalabrutinib effective sample size after matching	[redacted]	[redacted]	79
Progression free survival: HR (95% CI)			
Prior to MAIC adjustment (naïve comparison)	[redacted]	[redacted]	0.76 (0.39, 1.51)
After MAIC adjustment	[redacted]	[redacted]	0.92 (0.44, 1.95)
Overall survival: HR (95% CI)			
Prior to MAIC adjustment (naïve comparison)	[redacted]	[redacted]	0.64 (0.26, 1.57)
After MAIC adjustment	[redacted]	[redacted]	0.73 (0.27, 2.02)
Overall response rate: OR (95% CI)			
Prior to MAIC adjustment (naïve comparison)	[redacted]	[redacted]	1.2 (0.5, 2.9)
After MAIC adjustment	[redacted]	[redacted]	0.9 (0.4, 2.1)

ACAL = acalabrutinib; CI = confidence interval; HR = hazard ratio; IBR = ibrutinib; MAIC = matching adjusted indirect comparison; OBI = obinutuzumab; OR = odds ratio; VEN = venetoclax.

Source: Table 2.41, p.91; Table 2.42, p.92; Table 2.43, p.92; Table 2.44, p.92 of the submission.

[1] For the MAIC of acalabrutinib monotherapy versus ibrutinib monotherapy, 43 out of 179 patients in the acalabrutinib arm were excluded; for the MAIC of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab, 96 out of 179 patients in the acalabrutinib + obinutuzumab arm were excluded; for the MAIC of acalabrutinib monotherapy versus venetoclax + obinutuzumab, 83 out of 179 patients in the acalabrutinib monotherapy arm were excluded. The underlying reasons for exclusion were not adequately detailed in the submission.

6.33 The PBAC noted that a large number of patients were excluded from the MAIC analyses (96 out of 179) in the acalabrutinib + obinutuzumab arm for the comparison versus venetoclax + obinutuzumab; 83 out of 179 patients in the acalabrutinib monotherapy arm for the comparison versus venetoclax + obinutuzumab; 43 out of 179 patients in the acalabrutinib arm for the comparison versus ibrutinib monotherapy). While these exclusions are likely to be related to differences between the trials in eligibility criteria, the underlying reasons were not adequately documented in the submission.

6.34 Matching for the selected variables resulted in an effective sample size of 79 patients for the comparison of acalabrutinib with ibrutinib, 43patients for the comparison of acalabrutinib + obinutuzumab and venetoclax + obinutuzumab, and 51patients for the comparison of acalabrutinib and venetoclax + obinutuzumab, suggesting poor overlap between the trial populations. Post-matching characteristics for variables not chosen for matching were not provided and therefore, the impact of the matching on baseline variables that were not included in the MAIC is unclear. Due to the interdependence of variables, and different weights applied to each patient, matching of specific characteristics is likely to affect the distribution of other characteristics. It was unclear whether all relevant prognostic and effect modifier variables were identified.

6.35 In each of the comparisons for progression free survival and overall survival, there was no statistically significant difference between treatments prior to matching and results remained statistically non-significant after matching. A non-inferiority margin was not proposed in the submission for progression free survival or overall survival. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals are wide and likely to include clinically important differences. The results should be interpreted with caution due to the low effective sample size in the acalabrutinib arms after matching.

Comparative harms

6.36 Table 9 summarises the results of safety outcomes for the ELEVATE-TN trial at the interim analysis.

Table 9: Summary of adverse events for the ELEVATE-TN trial at the interim analysis

	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)
Grade ≥ 3 AE, n (%)	125 (70.2%)	89 (49.7%)	118 (69.8%)
Serious AE, n (%)	69 (38.8%)	57 (31.8%)	37 (21.9%)
Discontinuation due to AE, n (%)			
- Acalabrutinib	19 (10.7%)	17 (9.5%)	-
- Obinutuzumab	11 (6.2%)	-	10 (5.9%)
- Chlorambucil	-	-	24 (14.2%)
AE leading to death, n (%)	4 (2.2%)	6 (3.4%)	10 (5.9%)
Treatment-related AE, n (%)	144 (80.9%)	118 (65.9%)	154 (91.1%)
Any AE, n (%)	171 (96.1%)	170 (95.0%)	167 (98.8%)
Grade ≥ 3 AE incidence > 2%, n (%)			
- Neutropenia	53 (29.8%)	17 (9.5%)	70 (41.4%)
- Thrombocytopenia	15 (8.4%)	5 (2.8%)	20 (11.8%)
- Anaemia	10 (5.6%)	12 (6.7%)	12 (7.1%)
- Febrile neutropenia	3 (1.7%)	2 (1.1%)	9 (5.3%)
- Diarrhoea	8 (4.5%)	1 (0.6%)	3 (1.8%)
- Upper respiratory tract infection	4 (2.2%)	0	1 (0.6%)
- Pneumonia	10 (5.6%)	4 (2.2%)	3 (1.8%)
- Infusion-related reaction	4 (2.2%)	0	9 (5.3%)
- Alanine aminotransferase increased	5 (2.8%)	1 (0.6%)	3 (1.8%)
- Neutrophil count decreased	2 (1.1%)	0	5 (3.0%)
- Tumour lysis syndrome	2 (1.1%)	0	13 (7.7%)
- Syncope	4 (2.2%)	2 (1.1%)	1 (0.6%)
- Hypertension	5 (2.8%)	4 (2.2%)	5 (3.0%)

ACAL = acalabrutinib; AE = adverse event; CH =, chlorambucil; OBI = obinutuzumab.

Source: Table 2.28, pp77-78, Table 2.29, pp78-79; Table 2.30, pp79-80; Table 2.31, p.81; Table 2.32, pp82-83; Table 2.33, p.83; Table 2.34, p.84 of the submission.

6.37 Most patients in each treatment arm experienced at least one treatment-emergent adverse event. Serious adverse events were higher in the acalabrutinib + obinutuzumab (39%) and acalabrutinib monotherapy (32%) arms, compared to the chlorambucil + obinutuzumab arm (22%). Grade ≥ 3 adverse events were higher in the acalabrutinib + obinutuzumab (70%) and chlorambucil + obinutuzumab arms (70%) compared to the acalabrutinib monotherapy arm (50%). Treatment-related adverse

events were higher in the chlorambucil + obinutuzumab arm (91%), compared to the acalabrutinib + obinutuzumab arm (81%) and acalabrutinib monotherapy arm (66%).

6.38 The most commonly reported adverse events in the acalabrutinib + obinutuzumab arm (> 20%) were headache (40%), diarrhoea (39%), neutropenia (32%), fatigue (28%), contusion (24%), arthralgia (22%), cough (22%), upper respiratory infection (21%) and nausea (20%). The most commonly reported adverse events in the acalabrutinib monotherapy arm (> 20%) were headache (37%), diarrhoea (35%) and nausea (22%).

6.39 The PSCR stated that despite the longer treatment duration of acalabrutinib-based treatments (ongoing until disease progression) compared to chlorambucil (up to 24 weeks), the trial evidence demonstrated that the incidence of treatment related adverse events, any adverse events and adverse events resulting in death were higher in the chlorambucil + obinutuzumab arm. In addition, the reporting periods for adverse event follow-up were biased against the acalabrutinib-based arms (28 months, compared to 6 months for chlorambucil). The ESC noted that ≥ Grade 3 adverse events and serious adverse events were higher for the acalabrutinib-based therapies.

Matching adjusted indirect comparisons (MAICs)

6.40 The submission presented MAICs for selected adverse events for comparisons of acalabrutinib with ibrutinib, acalabrutinib + obinutuzumab and venetoclax + obinutuzumab, and acalabrutinib and venetoclax + obinutuzumab. The submission did not adequately justify the application of the MAIC methodology to adverse event data. The MAICs were conducted by matching patient characteristics that were considered to be prognostic and treatment effect modifier variables for CLL/SLL disease. These variables may not be relevant to the occurrence of adverse events. This approach has not been validated and is unlikely to be reliable and there was inadequate documentation on the selection of adverse events included in the MAIC. Therefore, the results should be interpreted with caution.

6.41 For the MAIC of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab, there was a statistically significant difference favouring acalabrutinib + obinutuzumab for infusion reaction, and favouring venetoclax + obinutuzumab for leukopenia and neutropenia prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib + obinutuzumab and venetoclax + obinutuzumab). After MAIC adjustment, the differences remained statistically significant.

6.42 For the MAIC of acalabrutinib monotherapy versus venetoclax + obinutuzumab, there was a statistically significant difference favouring acalabrutinib for febrile neutropenia, infusion reaction, neutropenia, diarrhoea and thrombocytopenia, and favouring venetoclax + obinutuzumab for leukopenia prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib and venetoclax + obinutuzumab). After MAIC adjustment, there was a statistically significant difference favouring

acalabrutinib for infusion reaction, neutropenia, diarrhoea, thrombocytopenia and infections, and favouring venetoclax + obinutuzumab for leukopenia.

6.43 For the MAIC of acalabrutinib monotherapy versus ibrutinib monotherapy, there was a statistically significant difference favouring acalabrutinib for pyrexia (any grade), hypertension (any grade), major haemorrhage (any grade), fatigue (any grade), peripheral oedema (any grade), atrial fibrillation (Grade 3/4), and infections (Grade 3/4) prior to MAIC adjustment (i.e. based on a naïve comparison of acalabrutinib monotherapy and ibrutinib monotherapy). After MAIC adjustment, the difference in these outcomes remained statistically significant.

6.44 As per the comparison with chlorambucil + obinutuzumab, the PSCR noted that despite the longer treatment duration for acalabrutinib-based therapies compared to venetoclax (up to 48 weeks), the safety profile for acalabrutinib + obinutuzumab was comparable to venetoclax + obinutuzumab.

Benefits/harms

6.45 On the basis of the direct evidence presented in the submission, for every 100 patients treated with acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab:

- Approximately 46 additional patients will remain progression free at two years.
- Approximately 12 fewer patients will experience life-threatening or severe neutropenia.
- Approximately 7 fewer patients will experience life-threatening or severe tumour lysis syndrome.
- Approximately 4 additional patients will experience life-threatening or severe pneumonia.

6.46 On the basis of the direct evidence presented in the submission, for every 100 patients treated with acalabrutinib monotherapy in comparison with chlorambucil + obinutuzumab:

- Approximately 41 additional patients will remain progression free at two years.
- Approximately 32 fewer patients will experience life-threatening or severe neutropenia.
- Approximately 9 fewer patients will experience life-threatening or severe thrombocytopenia.
- Approximately 8 fewer patients will experience life-threatening or severe tumour lysis syndrome.
- Approximately 5 fewer patients will experience a life-threatening or severe infusion-related reaction.

Clinical claim

6.47 The submission described acalabrutinib + obinutuzumab as superior in terms of efficacy, and no worse in terms of safety compared to chlorambucil + obinutuzumab.

- The ESC considered that the efficacy claim was adequately supported. Based on the results of the ELEVATE-TN trial, treatment with acalabrutinib + obinutuzumab was associated with statistically significant improvements in progression free survival and overall response rates compared to chlorambucil + obinutuzumab. There was no statistically significant difference in overall survival. The ESC noted that the efficacy data were immature and considered that more mature data would provide further certainty to the magnitude of the clinical benefit.
- The ESC considered that the safety claim was not adequately supported. Treatment with acalabrutinib + obinutuzumab was associated with a similar incidence of Grade ≥ 3 adverse events, a higher incidence of serious adverse events, and a lower incidence of treatment-related adverse events compared to chlorambucil + obinutuzumab. However, the ESC did note that differences in treatment duration were likely to impact overall numbers of adverse events (treatment with acalabrutinib is ongoing until disease progression or unacceptable toxicity whereas treatment with chlorambucil was for a fixed treatment duration of 24 weeks).
- Despite the PSCR providing results from a post-hoc analysis which demonstrated that acalabrutinib + obinutuzumab was associated with a greater progression free survival compared to acalabrutinib monotherapy, the ESC considered that it remained unclear whether the evidence presented in the submission adequately supported the use of acalabrutinib in combination with obinutuzumab rather than acalabrutinib monotherapy, given the increased risk of adverse events associated with combination therapy.

6.48 The PBAC considered the claim that acalabrutinib + obinutuzumab was superior compared to chlorambucil + obinutuzumab in terms of comparative efficacy was reasonable; however, due to the immaturity of the data, the magnitude of the benefit was uncertain.

6.49 In terms of safety, the PBAC considered that acalabrutinib + obinutuzumab was likely to result in similar safety outcomes compared to chlorambucil + obinutuzumab.

6.50 The submission described acalabrutinib monotherapy as superior in terms of efficacy and safety compared to chlorambucil + obinutuzumab.

- The ESC considered that the efficacy claim was adequately supported. Based on the results of the ELEVATE-TN trial, treatment with acalabrutinib monotherapy was associated with statistically significant improvements in progression free survival compared to chlorambucil + obinutuzumab, but no statistically significant differences in overall response rates or overall survival. The ESC noted that the efficacy data were immature and considered that more mature data would provide further certainty to magnitude of the clinical benefit.
- The ESC considered that the safety claim was not adequately supported. Treatment with acalabrutinib was associated with lower incidence of Grade ≥ 3 adverse events, a lower incidence of treatment-related adverse events, and a

higher incidence of serious adverse events compared to chlorambucil + obinutuzumab. However, the ESC did note that differences in treatment duration were likely to impact overall numbers of adverse events (treatment with acalabrutinib is ongoing until disease progression or unacceptable toxicity whereas treatment with chlorambucil was for a fixed treatment duration of 24 weeks).

6.51 The PBAC considered that the claim that acalabrutinib monotherapy was superior compared to chlorambucil + obinutuzumab in terms of comparative efficacy was reasonable; however, due to the immaturity of the data, the magnitude of the benefit was uncertain.

6.52 In terms of safety, the PBAC considered that acalabrutinib monotherapy was likely to result in superior safety outcomes compared to chlorambucil + obinutuzumab.

6.53 The submission described acalabrutinib monotherapy as non-inferior in terms of effectiveness, and superior in terms of safety compared to ibrutinib monotherapy among patients with a 17p deletion. Although the ESC considered that the outcomes of BTK inhibitors in patients with 17p deletion was likely to be similar to the outcomes in patients without 17p deletion this claim was not supported due to the following considerations:

- The results of the unanchored MAIC of acalabrutinib versus ibrutinib based on the full trial populations for the ELEVATE-TN and RESONATE-2 trials were highly uncertain. Matching of the selected prognostic and treatment effect modifier variables resulted in an effective sample size of 79, suggesting poor overlap between the trial populations. It was unclear whether all relevant prognostic and treatment effect modifier variables were identified and matched in the analysis.
- No non-inferiority margin for progression free survival or overall survival was proposed. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals were wide and may include a clinically important difference.
- The results of the unanchored MAICs of selected safety outcomes were unreliable, as the submission did not adequately justify the application of the MAIC methodology (based on adjustment for CLL/SLL disease prognostic and treatment effect modifier variables) to specific adverse event outcomes. The ESC noted that in considering acalabrutinib in the RR setting, the PBAC had previously considered that in terms of safety, acalabrutinib was likely to be non-inferior to ibrutinib (paragraph 7.10, acalabrutinib Public Summary Document (PSD), March 2020). The ESC considered that acalabrutinib monotherapy would similarly be non-inferior in terms of safety to ibrutinib in the newly diagnosed setting.

6.54 The PBAC considered that the clinical claims describing acalabrutinib monotherapy as non-inferior in terms of effectiveness and superior in terms of safety compared to ibrutinib were not adequately supported by the data. The PBAC considered that the

MAIC analyses were highly uncertain due to the low sample sizes and concerns whether all relevant prognostic and effect modifier variables were identified.

6.55 The submission described acalabrutinib + obinutuzumab as non-inferior in terms of progression free survival and overall survival but with a higher objective response rate compared to the supplementary comparator, venetoclax + obinutuzumab, and non-inferior in terms of safety compared to venetoclax + obinutuzumab. The submission described acalabrutinib monotherapy as non-inferior in terms of efficacy, and superior in terms of safety compared to venetoclax + obinutuzumab. The ESC considered that these claims were not adequately supported due to the following considerations:

- There were major differences between the ELEVATE-TN and CLL-14 trials in eligibility criteria, and a large number of patients were excluded from the MAIC analyses.
- The results of the unanchored MAIC analyses were highly uncertain. Matching for the selected variables resulted in an effective sample size of 43for the acalabrutinib + obinutuzumab comparison, and 51 for the acalabrutinib monotherapy comparison, indicating poor overlap between the included trial populations. Additionally, it was unclear whether all relevant prognostic and treatment effect modifier variables were identified and matched in the analysis.
- No non-inferiority margin for progression free survival or overall survival was proposed. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals were wide and may include a clinically important difference.
- The results of the unanchored MAICs of selected safety outcomes were unreliable, as the submission did not adequately justify the application of the MAIC methodology (based on adjustment for CLL/SLL disease prognostic and treatment effect modifier variables) to specific adverse event outcomes.
- The ESC noted that differences in treatment duration are likely to impact overall numbers of adverse events. Treatment with acalabrutinib is ongoing until disease progression or unacceptable toxicity; whereas, in the venetoclax + obinutuzumab regimen, venetoclax was administered for a fixed treatment duration of 12 cycles (48 weeks).

6.56 The PBAC considered that the clinical claims versus venetoclax + obinutuzumab were not adequately supported by the data as the MAICs were highly uncertain.

Economic analysis

6.57 The submission presented a cost-effectiveness analysis comparing acalabrutinib monotherapy or acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab; and a cost-minimisation analysis comparing acalabrutinib monotherapy with ibrutinib monotherapy.

6.58 The poor documentation of many variables (transitions, utilities and costs) made it difficult to assess the validity of the model.

Cost effectiveness analysis

6.59 For previously untreated CLL patients unsuitable for treatment with a purine analogue, the submission presented a modelled economic evaluation comparing:

- sequential treatment with acalabrutinib monotherapy or acalabrutinib with obinutuzumab combination therapy followed by venetoclax with rituximab (80%) or idelalisib with rituximab (20%) followed by best supportive care, and
- sequential treatment with chlorambucil with obinutuzumab combination therapy followed by ibrutinib monotherapy followed by best supportive care.

The economic evaluation was based on the ELEVATE-TN trial with additional modelled data. The economic evaluation was presented as a cost-utility analysis.

6.60 The modelling of sequential treatment in the submission assumed that first-line treatment with acalabrutinib would modify second-line treatment options. This may be reasonable; however, the assumed differences in utilisation, efficacy and cost of second-line treatment options for each modelled arm were not adequately justified in the submission. In particular, the unsupported assumption that venetoclax with rituximab will only be used after acalabrutinib but not chlorambucil was a key driver of the economic model. The PSCR considered that it was unlikely that patients who had received chlorambucil + obinutuzumab in the first-line setting would receive venetoclax + rituximab in the second-line based on (i) the current low PBS utilisation of venetoclax + rituximab in the RR setting; and (ii) clinical opinion that venetoclax + rituximab is used post BTK inhibitor failure, meaning that ibrutinib is the preferred second-line treatment for these patients.

Table 10: Summary of model structure, key inputs and rationale

Component	Description
Treatments	• Acalabrutinib or acalabrutinib + obinutuzumab, followed by venetoclax + rituximab (80%) or idelalisib + rituximab (20%), followed by best supportive care • Chlorambucil + obinutuzumab combination therapy followed by ibrutinib monotherapy followed by best supportive care
Time horizon	20 years versus 30 months in the ELEVATE-TN trial
Outcomes	QALYs
Methods used to generate results	Markov state transition model
Health states	6 health states (progression free on-treatment, progression free off-treatment, drug holiday, second-line treatment, best supportive care and dead). The model uses tunnel states to track treatment history.
Cycle length	28 days (with half-cycle correction)
Transition probabilities	• Transition probabilities (based on time-to-discontinuation, time-to-progression and time-to-death) from the progression free states were derived from the ELEVATE-TN trial with additional assumptions. • The transition probability from the drug holiday to second-line treatment was based on the assumption that second-line treatment would be delayed for 3 cycles in all progressed patients. • Transition probabilities from drug holiday to death were assumed to be the same as the transition probabilities from second-line treatment to death. • Transition probabilities (based on PFS, OS) from the second-line treatment state were derived from published RR trials for venetoclax with rituximab (MURANO), ibrutinib monotherapy (RESONATE), idelalisib with rituximab (using proxy data from ASCEND) with additional assumptions. • Transition probabilities (based on overall survival) from the best supportive care health state were derived from Australian life tables with a mortality multiplier for CLL disease (Cunha-Bang 2016)
Extrapolation method	<u>First-line treatment</u> • Time to treatment discontinuation was independently extrapolated for acalabrutinib monotherapy (using a generalised gamma function) and acalabrutinib + obinutuzumab (using a log-normal function). The submission assumes no treatment discontinuations in the first 6 cycles for chlorambucil + obinutuzumab, with all patients discontinuing treatment after 6 cycles. • Time to progression was independently extrapolated for acalabrutinib monotherapy (using an exponential function), acalabrutinib + obinutuzumab (using a log-normal function) and chlorambucil + obinutuzumab (using a Weibull function). • Time to death was independently extrapolated for acalabrutinib monotherapy (using an exponential function), acalabrutinib + obinutuzumab (using a Gompertz function) and chlorambucil + obinutuzumab (using a Weibull function). <u>Second-line treatment</u> • PFS was independently extrapolated for venetoclax + rituximab (using a Weibull function), idelalisib + rituximab (using a log-logistic function) and ibrutinib (using an exponential function). • OS was independently extrapolated for venetoclax + rituximab (using an exponential function), idelalisib + rituximab (using an exponential function) and ibrutinib (using an exponential function). <u>Proportion of incremental costs and outcomes in modelled period</u> • For the acalabrutinib monotherapy vs chlorambucil with obinutuzumab comparison, 51.2% of incremental costs; 95.2% of incremental QALYs; and 97.0% of incremental life years are accrued in the extrapolated period (beyond 2.3 years, based on 30 cycles). • For the acalabrutinib with obinutuzumab vs chlorambucil with obinutuzumab comparison, 44.5% of incremental costs; 95.8% of incremental QALYs; and 98.2% of incremental life years are accrued in the extrapolated period (beyond 2.3 years, based on 30 cycles).

Component	Description
Health related quality of life	• Pre-progression utility values were based on mean utility value across all treatment arms in the ELEVATE-TN trial (0.817). • The utilities associated with progression (0.66 for drug holiday; 0.55 for second line treatment) and subsequent therapy (0.42 for best supportive care) were derived from a published utility study of CLL from the perspective of the UK general public (Kosmas 2015). • AE disutility values were estimated based on various published sources identified primarily through NICE appraisal documents (ID764, ID838, ID1097) and a recent conference poster presenting a utility model for ivosidenib in RR AML (Boscoe 2018).
Costs	• Acalabrutinib drug costs were based on the proposed effective price including the effects of both an SPA rebate and an RSA treatment cap. The drug costs for obinutuzumab, venetoclax, ibrutinib and idelalisib were estimated from published DPMQ/DPMA assuming both an SPA rebate and RSA treatment cap, when relevant. The drug costs for rituximab was based on the published DPMA. • AE costs were primarily estimated based on AR-DRG items with additional estimates from an unpublished thesis (Pearce 2013) and additional assumptions. • Disease management costs were estimated based on expert advice on health resource use from a NICE appraisal document (ID1097) and costings based on MBS and AR-DRG items. • Terminal care costs were estimated based on a review of hospital claims data from New South Wales for older persons in their last year of life (Kardamanidis 2007).

AE = adverse event; AML = acute myeloid leukaemia; AR-DRG = Australian refined diagnosis related group; CLL = chronic lymphocytic leukaemia; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; RR = relapsed and/or refractory; RSA = risk sharing arrangement; SPA = special pricing arrangement; UK = United Kingdom

Source: Table 3.1 (p 101) of the submission

6.61 The submission nominated a 20-year time horizon for the economic analysis on the basis that this was appropriate to capture the majority of costs and benefits in a population with previously untreated CLL. However, the PBAC has previously considered a 10-year time horizon to be appropriate for previously untreated patients unsuitable for a purine analogue (Obinutuzumab PSD, July 2014 PBAC meeting; Ibrutinib PSD, November 2017 PBAC meeting). The PBAC previously noted that longer time horizons may be unreliable due to the immaturity of available clinical trial data and the fragility of patient populations, i.e. patients > 70 years of age who will likely have comorbidities (Ibrutinib PSD, November 2017 PBAC meeting).

6.62 The data from the ELEVATE-TN trial were relatively immature compared to the modelled timeframe (median 2.3 years versus 20 years). As a consequence, most of the survival functions presented in the submission provided very similar goodness-of-fit estimates but lead to widely divergent extrapolated estimates. The differences between these estimates were substantial, with major consequences on the interpretation of long-term treatment effects (see sensitivity analyses).

6.63 The PSCR considered that a 20 year time horizon was appropriate. However, the ESC noted that the proportions of acalabrutinib monotherapy and acalabrutinib + obinutuzumab patients alive at 20 years (approximately 25% to 30% respectively) were unlikely considering patients entered the model at 70 years, consisted of 65% males and were less fit than the general population. The ESC considered that a time horizon of 15 years would mitigate some of the uncertainty in the model, although considered that the extrapolation functions should also be revised to provide more

plausible estimates of long-term survival. The PBAC recalled that the March 2020 submission for use of venetoclax in the first-line CLL/SLL setting applied a 10 year time horizon.

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

Table 11: Key drivers of the model

Description	Method/Value	Impact
Overall survival benefit	The model generates differences in OS between treatments that is not supported by data presented in the submission or in previous PBAC considerations of treatments for RR disease. In first-line therapy, the submission used separate time to death curves for each treatment arm, which implicitly assumes differences in survival between therapies, which is not supported by the available clinical data from the ELEVATE-TN trial. The PSCR stated that the significant improvement in PFS (PFS at 36 months: acalabrutinib + obinutuzumab = 89.6%; acalabrutinib monotherapy = 63.9%; chlorambucil + obinutuzumab = 31.3%) could be reasonably expected to translate into an OS benefit as the data matured. In addition, the PSCR noted that post-progression crossover to acalabrutinib occurred in approximately 25% of chlorambucil + obinutuzumab patients. The PBAC noted that the survival differences in the first-line setting were not supported by data from the ELEVATE-TN trial. Transition probabilities from the second-line treatment state were derived from published RR trials for venetoclax with rituximab (MURANO), ibrutinib monotherapy (RESONATE), and idelalisib with rituximab (using proxy data from ASCEND).These trials appear to have limited applicability to the modelled population as they typically included younger patients, with multiple lines of prior therapy and had prior exposure to a purine analogue. Further, there were substantial differences in age, number of prior therapies and the presence/absence of cytogenetic abnormalities between the second-line treatment arms, which will affect the survival estimates from each treatment arm leading to modelled differences between second-line treatments that may not be reflective of their comparative efficacy. The extrapolated survival curves suggested that there were substantial differences in survival between second-line therapies (ibrutinib monotherapy had superior PFS; venetoclax with rituximab had superior OS). Noting that the PBAC has previously considered that venetoclax with rituximab was non-inferior to ibrutinib monotherapy in the RR setting (para 6.40, Venetoclax PSD, November 2018 PBAC meeting), the ESC considered that ibrutinib and venetoclax + rituximab should have the same effectiveness outcomes and costs in the base case. The pre-PBAC response considered that this was appropriate. The death transition probabilities for second-line therapies were based on OS estimates (includes deaths with and without progression). This approach was inconsistent with the estimation of transition probabilities for first line therapies (which were based on deaths without progression). The estimation of death transitions from OS was inappropriate as the model incorporates three lines of therapy (first line, second line, BSC) and therefore post-progression deaths should be excluded from the second-line transition probabilities (as post-progression deaths will occur in the BSC phase). The ESC noted that the differences in how deaths were modelled in the first-line compared to the second-line resulted in inconsistent patterns in mortality rates (see Figure 4). Most of the survival functions presented in the submission provided very similar goodness-of-fit estimates but lead to widely divergent extrapolated estimates. As a consequence, extrapolated survival in the model was highly uncertain.	High, favours acalabrutinib

<table>
<tr><th>Description</th><th>Method/Value</th><th>Impact</th></tr>
<tr><td>Utilities</td><td>Pre-progression utility values were based on the mean utility value across all treatment arms in the ELEVATE-TN trial. The utilities associated with progression and subsequent therapy were derived from a published utility study (Kosmas 2015).

The health state utility values used in the model were not adequately supported, with the ESC considering that the major differences between trial based (ELEVATE-TN) and published estimates (Kosmas 2015) indicated that the two data sources could not be directly combined to estimate utility losses associated with progression and lines of therapy. Re-anchoring values for progression and subsequent lines of therapy to the Kosmas 2015 initial therapy values resulted in substantially smaller disutilities associated with progression and subsequent lines of therapy (see Table 11.1). The ESC and PBAC considered that the values re-anchored to the oral initial therapy state were the most reasonable.

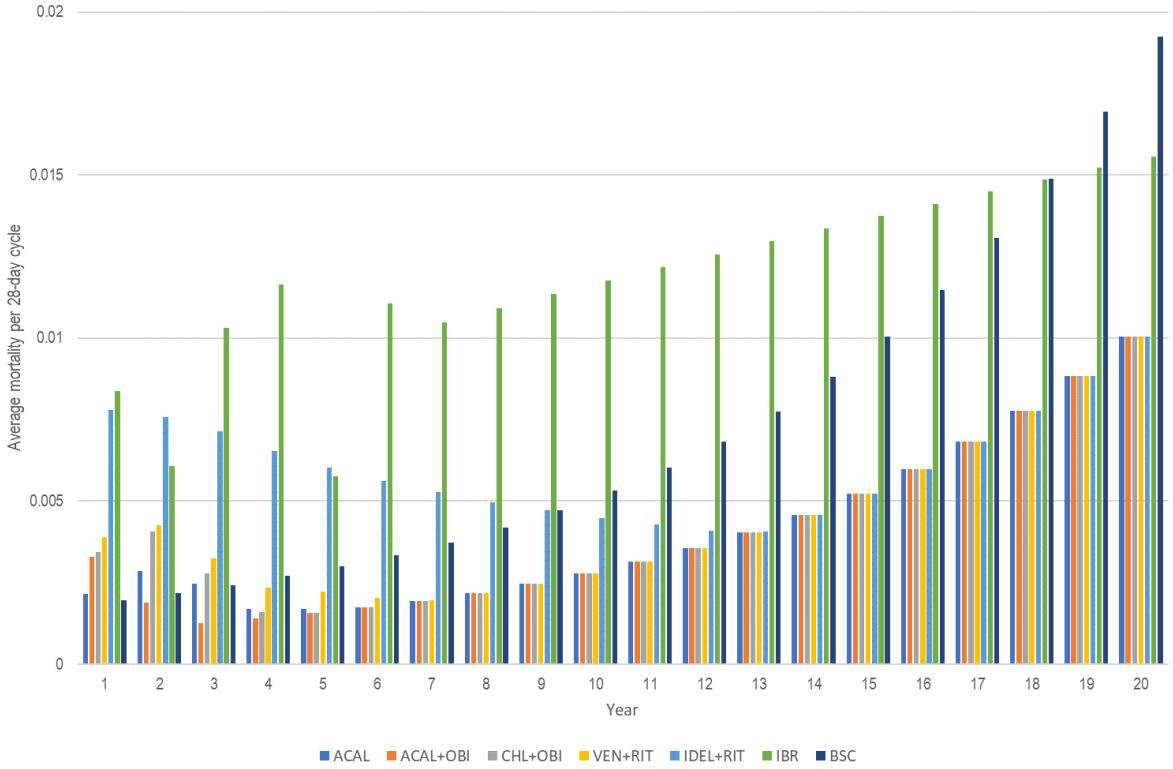
Table 11.1: Comparison of utility values
<table>
<tr><th>Health state</th><th>Submission</th><th>Re-anchored to IV initial therapy state</th><th>Re-anchored to oral initial therapy state</th></tr>
<tr><td>Progression free on treatment</td><td>0.817</td><td>0.817</td><td>0.817</td></tr>
<tr><td>Progression free off treatment</td><td>0.817</td><td>0.817</td><td>0.817</td></tr>
<tr><td>Drug holiday</td><td>0.660</td><td>0.807</td><td>0.777</td></tr>
<tr><td>Second-line treatment</td><td>0.550</td><td>0.697</td><td>0.657</td></tr>
<tr><td>Best supportive care</td><td>0.420</td><td>0.567</td><td>0.527</td></tr>
</table>
IV = intravenous
Source = Source: Table 3.21 (p 144), Table 3.22 (p 144) of the submission</td><td>Moderate, favours acalabrutinib</td></tr>
<tr><td>Disconnect between time to treatment discontinuation and time to progression</td><td>The submission assumed that the risk of progression or death does not change depending on whether patients are receiving active therapy with acalabrutinib. In the model, patients in the progression free off-treatment state in the acalabrutinib monotherapy and acalabrutinib with obinutuzumab arms spend on average 9.2 and 10.6 years, respectively, progression free while not receiving treatment. The PSCR stated that patients occupied the progression free off-treatment state for a mean of 1.3 and 1.5 years respectively (as demonstrated by the orange lines in Figures 5 and 6). However, the ESC noted that this was based on the average time spent in this state for the entire cohort of patients, whereas the times of 9.2 and 10.6 years were based on the average time spent in this state for the patients who discontinued therapy.
Although the evaluators noted that the time in the progression free off-treatment state was inconsistent with existing data from BTK inhibitors which suggested accelerated disease progression after the cessation of therapy (NCCN CLL guidelines version 4.2020), the ESC noted that this evidence was from clinical trials in the RR setting. The ESC considered that the effect of BTK inhibitors on disease progression in the first-line setting was unknown.</td><td>High, favours acalabrutinib</td></tr>
<tr><td>Impact of SPAs and RSAs</td><td>The submission proposed a SPA for acalabrutinib (based on a [redacted]% rebate on the published price) and used the effective price in the model. The submission noted that obinutuzumab, ibrutinib, venetoclax and idelalisib are subject to SPAs and assumed an effective prices based on a 30% rebate on their published prices. The submission proposed a RSA capping government expenditure on acalabrutinib to [redacted] cycles of therapy (approximately [redacted] years). The submission noted that ibrutinib, venetoclax and idelalisib are also subject to RSAs, which the submission assumed were based on a maximum duration treatment cap. The treatment cap estimates calculated in the submission were poorly documented and could not be validated during the evaluation. The assumed rebates and treatment caps may not be reflective of the SPAs and RSAs in place for these therapies and will affect the estimated cost-effectiveness of acalabrutinib.</td><td>Unclear impact</td></tr>
</table>

BSC = best supportive care; BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukaemia; ESC = Economic Sub-Committee; IV = intravenous; NCCN = National Comprehensive Cancer Network; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory

Committee; PFS = progression free survival; PSCR = pre-Sub-Committee Response; PSD = Public Summary Document; RR = relapsed and/or refractory; RSA = risk sharing arrangement; SPA = special pricing arrangement
Source: Constructed during the evaluation

6.65 The ESC and PBAC noted that differences in how first and second-line mortality was modelled resulted in inconsistencies which lacked face validity. The average mortality rates for patients receiving first-line (acalabrutinib, acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab) and second-line (venetoclax + rituximab, idelalisib + rituximab and ibrutinib) treatments were higher than for patients receiving third-line treatment (best supportive care) for the first two years of the model, and with mortality rates for patients treated with ibrutinib in the second-line setting remaining higher than for patients treated with best supportive care until Year 18 (see Figure 4).

Figure 4: Average mortality rates used in the economic model for different lines of therapy.

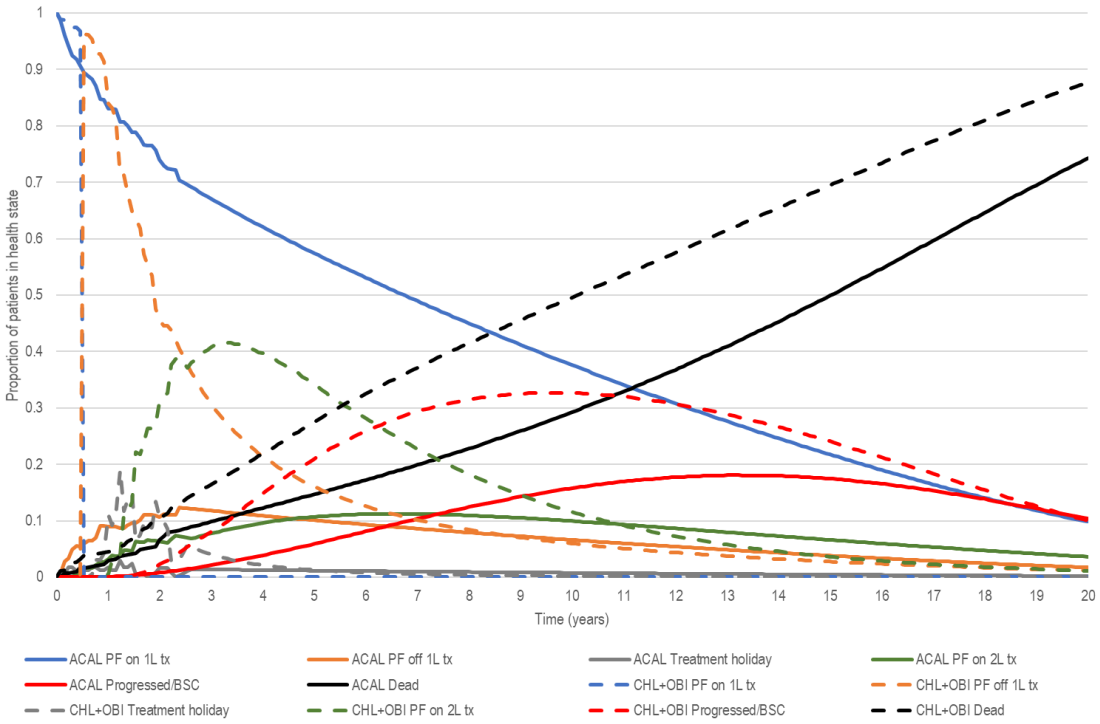


ACAL = acalabrutinib; BSC = best supportive care; CHL = chlorambucil; IBR = ibrutinib; IDEL = idelalisib; OBI = obinutuzumab; RIT = rituximab; VEN = venetoclax
Source: Constructed during the evaluation based on data in the 'Acalabrutinib (Calquence)_CEA_model calculations_10Mar20' Excel spreadsheet included in the submission

6.66 An additional limitation of the economic evaluation was the inadequate approach to modelling adverse events (based on incidence and applied in the first cycle only) given the substantial difference in modelled treatment exposure between arms (approximately 8.9 years versus 6 months). Additionally, the submission inadequately justified the use of severe treatment-related events (which includes abnormal laboratory values) versus serious adverse events (which require hospitalisation). The PSCR stated that the approach to modelling adverse events was reasonable as the majority of adverse events occurred within the trial period.

6.67 Model traces indicate rapid separation between treatment arms in the proportion of patients who remain progression free after the first 6 months. A higher proportion of patients in the chlorambucil with obinutuzumab arm progress to second-line treatment and best supportive care, with a corresponding higher proportion of deaths in the chlorambucil with obinutuzumab arm.

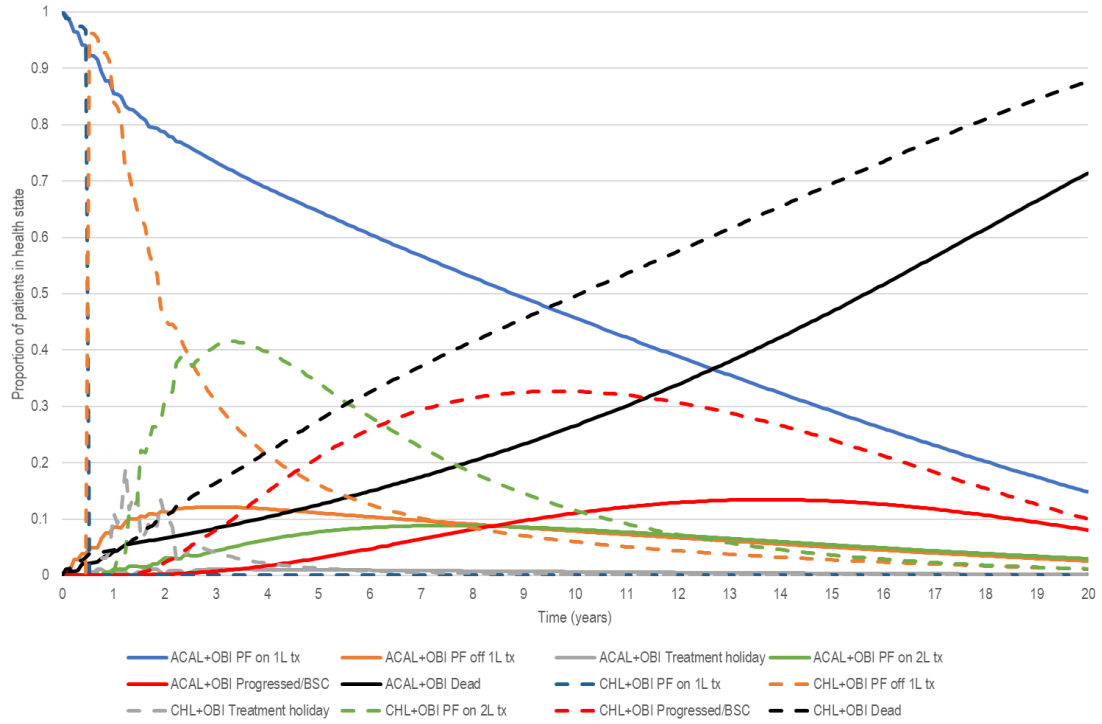
Figure 5: Model trace: acalabrutinib monotherapy versus chlorambucil + obinutuzumab



ACAL = acalabrutinib; BSC = best supportive care; CHL = chlorambucil; OBI = obinutuzumab; PF = progression free; tx = treatment; 1L = first-line; 2L = second-line

Source: Constructed during the evaluation using the Acalabrutinib (CALQUENCE)_1L CLL_PBAC CE Model_FINAL TreeAge model provided with the submission

Figure 6: Model trace: acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab



ACAL = acalabrutinib; BSC = best supportive care; CHL = chlorambucil; OBI = obinutuzumab; PF = progression free; tx = treatment; 1L = first-line; 2L = second-line

Source: Constructed during the evaluation using the Acalabrutinib (CALQUENCE)_1L CLL_PBAC CE Model_FINAL TreeAge model provided with the submission

6.68 The results of the modelled economic evaluation using assumed effective prices for obinutuzumab, ibrutinib, venetoclax and idelalisib are summarised in Table 12.

Table 12: Results of the economic evaluation

Component	**ACAL mono**	**CHL + OBI**	**Increment**
Costs[a]	$[redacted]	$[redacted]	$[redacted]
QALYs	6.84	4.59	2.25
		Incremental cost per QALY gained	**$[redacted]**
Component	**ACAL + OBI**	**CHL + OBI**	**Increment**
Costs[a]	$[redacted]	$[redacted]	$[redacted]
QALYs	7.28	4.59	2.69
		Incremental cost per QALY gained	**$[redacted]**

ACAL = acalabrutinib; AEMP = approved ex-manufacturer price; CHL = chlorambucil; DPMQ = dispensed price for maximum quantity; OBI = obinutuzumab; QALY = quality adjusted life year

Source: Table 3.36 (p 156) of the submission

[a] Includes correction of acalabrutinib drug cost from effective AEMP to effective DPMQ

6.69 Based on the economic model:

- treatment with acalabrutinib monotherapy was associated with a cost per QALY gained of $45,000 to < $55,000/QALY compared to chlorambucil with obinutuzumab combination therapy.

- treatment with acalabrutinib and obinutuzumab combination therapy was associated with a cost per QALY gained of $55,000 to < $75,000/QALY compared to chlorambucil with obinutuzumab combination therapy.

6.70 The results of key univariate sensitivity analyses are summarised in Table 13.

6.71 The PSCR provided a number of alternate sensitivity analyses, including:

- a scenario (#1) where there was no difference in time to death in the first-line setting (i.e. time to death curve from acalabrutinib monotherapy was applied to each of the first-line treatment arms). The ESC noted that this differed from the analysis conducted during the evaluation which applied the time to death curve from the chlorambucil + obinutuzumab arm to each of the first-line treatments;
- a scenario (#2) in which the second-line efficacy of ibrutinib and venetoclax + rituximab were assumed to be equal and based on the ibrutinib arm of the RESONATE trial. The ESC noted that although the PSCR analysis assumed equal benefits, the costs of ibrutinib and venetoclax + rituximab in the second were not assumed to be equal. The ESC noted that this differed from the analysis conducted during the evaluation in which ibrutinib and venetoclax + rituximab were assumed to be equal by applying the costs and benefits of venetoclax + rituximab to all second-line patients. The pre-PBAC response agreed that the costs and efficacy of second-line therapies should be equal; and
- a scenario (#3) in which there was 100% venetoclax + rituximab utilisation in the second-line for acalabrutinib monotherapy and acalabrutinib + obinutuzumab patients.

Table 13: Results of sensitivity analyses

Analyses	ACAL versus CHL+OBI			ACAL+OBI versus CHL+OBI		
	Incr cost	Incr QALY	ICER	Incr cost	Incr QALY	ICER
Base case[a]	$[redacted]	2.25	$[redacted]	$[redacted]	**2.69**	$[redacted]
Time horizon (base case 20 years)						
10 years (130 cycles)	$[redacted]	1.38	$[redacted]	$[redacted]	1.60	$[redacted]
15 years (196 cycles)	$[redacted]	1.96	$[redacted]	$[redacted]	2.30	$[redacted]
First-line survival extrapolations (base case: individual extrapolated curves assumed differences in survival between treatment arms; extrapolation functions based on best AIC/BIC estimate)						
Patients treated with ACAL/ACAL + OBI experience progression 1 cycle after discontinuation (base case 9.2/10.6 years)	$[redacted]	1.86	$[redacted]	$[redacted]	2.24	$[redacted]
Most pessimistic TTP extrapolation curve for ACAL mono/ACAL + OBI (Gompertz)	$[redacted]	1.36	$[redacted]	$[redacted]	1.29	$[redacted]
Most optimistic TTP extrapolation curve for ACAL mono (lognormal)/ACAL + OBI (generalised gamma)	$[redacted]	2.52	$[redacted]	$[redacted]	2.89	$[redacted]
No difference in 1st-line survival (CHL + OBI arm time to death used for all treatments)	$[redacted]	2.04	$[redacted]	$[redacted]	2.38	$[redacted]
PSCR #1: No difference in 1st-line survival (ACAL mono arm time to death used for all treatments)	$[redacted]	2.12	$[redacted]	$[redacted]	2.47	$[redacted]
Second-line therapy (base case: acalabrutinib switches to venetoclax with rituximab - 80% or idelalisib with rituximab - 20%; chlorambucil with obinutuzumab switches to ibrutinib)						
Both treatment arms switch to venetoclax with rituximab 80% or idelalisib with rituximab 20%	$[redacted]	1.95	$[redacted]	$[redacted]	2.39	$[redacted]
Both treatment arms switch to venetoclax with rituximab 100%	$[redacted]	1.88	$[redacted]	$[redacted]	2.30	$[redacted]
Both treatment arms switch to idelalisib with rituximab 100%	$[redacted]	2.06	$[redacted]	$[redacted]	2.52	$[redacted]
PSCR #2: 2nd-line efficacy of ibrutinib and venetoclax + rituximab equal (ibrutinib effectiveness from RESONATE used)	$[redacted]	2.13	$[redacted]	$[redacted]	2.60	$[redacted]
PSCR #3: ACAL arms only receive 100% venetoclax + rituximab	$[redacted]	2.32	$[redacted]	$[redacted]	2.74	$[redacted]
Utilities (base case: progression free utility based on ELEVATE-TN, progression and subsequent line therapy based on Kosmas 2015)						
Utility values re-anchored to IV initial therapy state from Kosmas 2015	$[redacted]	1.89	$[redacted]	$[redacted]	2.22	$[redacted]
Utility values re-anchored to oral initial therapy state from Kosmas 2015	$[redacted]	1.99	$[redacted]	$[redacted]	2.35	$[redacted]
Treatment Costs (base case: acalabrutinib – effective DPMQ with 116 cycle cap)						
Remove cycle cap for acalabrutinib	$[redacted]	2.25	$[redacted]	$[redacted]	2.69	$[redacted]

ACAL = acalabrutinib; AEMP = approved ex-manufacturer price; AIC = Akaike information criterion; BIC = Bayesian information criterion; CHL = chlorambucil; DPMQ = dispensed price for maximum quantity; ICER = incremental cost effectiveness ratio; Incr = incremental; IV = intravenous; OBI = obinutuzumab; PSCR = pre-Sub-Committee Response; QALY = quality adjusted life year; TTP = time to progression
Source: Table 3.39 (p 159) of the submission

[a] Includes correction of acalabrutinib drug cost from effective AEMP to effective DPMQ

The redacted table shows ICERs in the range of $55,000 to < $75,000 to $115,000 to < $135,000.

6.72 The ESC, noting the large effect on the ICER of choice of time to progression extrapolation function, considered that the extrapolations in the model were highly uncertain.

6.73 The results of key multivariate sensitivity analyses are summarised in Table 15.

6.74 During evaluation an alternative base case was proposed. Table 14 provides a comparison of the alternative base case provided in the commentary and the revised alternative base case provided in the PSCR.

Table 14: A comparison of the alternative base case as provided in the commentary and the revised alternative base case provided in the PSCR

	No difference in time to death in 1st-line setting		2nd-line efficacy		Health state utilities
	Application of CHL + OBI curve to all arms	Application of ACAL mono curve to all arms	Application of costs and benefits of VEN + RITUX to all patients	Application of benefits only of IBR to VEN + RITUX patients	Re-anchored to oral therapy
Alternative base case	✓		✓		✓
PSCR alternative base case		✓		✓	✓

ACAL = acalabrutinib; CHL = chlorambucil; IBR = ibrutinib; OBI = obinutuzumab; PSCR = pre-Sub-Committee response; RITUX = rituximab; VEN = venetoclax

6.75 As noted in paragraph 6.71 the analysis presented in the PSCR assumed that ibrutinib and venetoclax + obinutuzumab would have the same survival benefit, but different costs. The ESC considered that this analysis was inappropriate and inconsistent with the PBACs previous decision to list venetoclax + rituximab on a cost-minimisation basis versus ibrutinib. Therefore, the PSCR analysis was replicated assuming the same benefit and costs for ibrutinib and venetoclax + rituximab.

6.76 The ESC considered that sensitivity analyses of the alternative base case and the PSCR alternative base case with time horizons of 15 and 10 years would be informative. The ESC noted that resultant ICERs would remain uncertain due to the extrapolation issues identified in paragraph 6.67.

Table 15: Results of multivariate sensitivity analysesa

Analyses	ACAL versus CHL+OBI			ACAL+OBI versus CHL+OBI		
	Incr cost	Incr QALY	ICER	Incr cost	Incr QALY	ICER
Alternative base case (evaluation)	**$**	**1.31**	**$**	**$**	**1.56**	**$**
+ 15 year time horizon (196 cycles)	$	1.08	$	$	1.26	$
+ 10 year time horizon (130 cycles)	$	0.71	$	$	0.82	$
+ most pessimistic TTP extrapolation curve for ACAL mono (Gompertz)	$	0.70	$	$	0.61	$
+ Most optimistic TTP extrapolation curve for ACAL mono (lognormal)	$	1.49	$	$	1.69	$
PSCR alternative base case (ESC corrected)b	**$**	**1.69**	**$**	**$**	**2.01**	**$**
+ 15 year time horizon (196 cycles)	$	1.43	$	$	1.68	$
+ 10 year time horizon (130 cycles)	$	0.96	$	$	1.11	$

ACAL = acalabrutinib; AEMP = approved ex-manufacturer price; CHL = chlorambucil; DPMQ = dispensed price for maximum quantity; ICER = incremental cost effectiveness ratio; Incr = incremental; OBI = obinutuzumab; PSCR = pre-Sub-Committee Response; QALY = quality adjusted life year; TTP = time to progression

Source: Table 3.39 (p 159) of the submission

[a] Includes correction of acalabrutinib drug cost from effective AEMP to effective DPMQ

[b] The analysis in the PSCR assumed that second-line therapies would have the same survival benefit (based on ibrutinib) but different costs (ibrutinib vs. venetoclax/idelalisib with rituximab) resulting in ICER of $55,000 to < $75,000 per QALY for acalabrutinib monotherapy and $75,500 to < $95,000 per QALY for acalabrutinib combination therapy. This analysis was inappropriate and inconsistent with PBACs previous recommendation to list venetoclax on a cost-minimisation basis versus ibrutinib. Therefore, the PSCR analysis was replicated assuming that both arms had the same second-line survival benefit and cost (based on ibrutinib).

The redacted table shows ICERs in the range of $75,000 to < $95,000 to $255,000 to < $355,000.

Cost minimisation analysis

6.77 The submission presented a cost minimisation analysis of acalabrutinib monotherapy versus ibrutinib monotherapy based on the claim of non-inferior effectiveness and superior safety in the subset of previously untreated CLL/SLL patients with 17p deletion. The submission did not include a cost-minimisation analysis of acalabrutinib + obinutuzumab versus ibrutinib monotherapy.

6.78 The submission proposed the following equi-effective doses:

Acalabrutinib 100 mg twice daily = ibrutinib 420 mg once daily.

6.79 The equi-effective doses of acalabrutinib and ibrutinib were based on the doses used in the ELEVATE-TN and RESONATE-2 trials. These doses are consistent with the doses recommended in the respective product information documents. For both acalabrutinib and ibrutinib, treatment is recommended to continue until disease progression or unacceptable toxicity.

6.80 The cost-minimisation analysis included costs associated with Grade 1/2 diarrhoea, and Grade 3/4 major haemorrhage, infections, and atrial fibrillation. Table 16 summarises the derivation of the adverse event costs included in the cost-minimisation analysis.

Table 16: Adverse event costs included in the cost-minimisation analysis.

	Cost	Acalabrutinib		Ibrutinib	
		Proportion[1]	Cost	Proportion[1]	Cost
Vomiting (Grade 1/2)	$44.10	3.1%	$1.36	7.0%	$3.10
Haemorrhage (Grade 3/4)	$6,770.29	0.8%	$51.49	2.5%	$168.09
Infection (Grade 3/4)	$5,243.46	5.2%	$274.73	9.9%	$520.73
Atrial fibrillation (Grade 3/4)	$3,995.48	0%	$0	1.7%	$66.13

MAIC = matching adjusted indirect comparison
Source: Table 3.43, p165; Table 3.44, p166; Table 3.45, p166; Table 3.46, p167 of the submission.
[1] The proportions of patients with adverse events were based on the MAIC analysis, adjusted for the 12 month duration of the analysis.

6.81 Based on the included adverse event costs and proportions, the estimated cost of treating adverse events was $327.58 for acalabrutinib and $758.05 for ibrutinib, a difference of $430.47.

6.82 The results of the cost minimisation analysis of acalabrutinib monotherapy versus ibrutinib monotherapy in the subset of previously untreated CLL/SLL patients with 17p deletion, using the published price of ibrutinib, are summarised in the table below.

Table 17: Derivation of the cost-minimised price for acalabrutinib based on the ibrutinib published price

	Ibrutinib	Acalabrutinib
Proposed equi-effective dose	420 mg daily for 12 months	100 mg twice daily for 12 months
Treatment cost (Ibrutinib)		
IBR 140 mg drug cost at AEMP (90 capsules per pack)	$8,633.29	-
IBR drug cost over 12 months (12.18 packs x $8,633.29)	$105,110.31	-
IBR adverse event costs over 12 months	$758.05	-
IBR total treatment costs over 12 months	$105,868.36	-
Cost-minimisation (Acalabrutinib)		
ACAL total treatment cost over 12 months	-	$105,868.36
ACAL adverse event costs over 12 months	-	$327.58
ACAL drug cost over 12 months ($105,868.36 - $327.58)	-	$105,540.78
ACAL 100 mg cost-minimised AEMP ($105,540.78 ÷ 13.04 packs)	-	$8,090.75
ACAL 100 mg cost-minimised DPMQ (56 capsules per pack)	-	$9,127.00

ACAL = acalabrutinib; AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; IBR = ibrutinib.
Source: Table 3.47, p168 of the submission; 'Acalabrutinib (CALQUENCE)_1L CLL_PBAC CM Model_FINAL' Excel workbook.

6.83 Based on the published price of ibrutinib, the cost-minimised DPMQ for acalabrutinib was $9,127.00.

6.84 The results of the cost-minimisation analysis are not reliable due to the following:

- The submission's claim of non-inferior efficacy and superior safety of acalabrutinib compared to ibrutinib in patients with 17p deletion was not supported.
- The submission's cost offsets were based on the adjusted adverse event rates reported for the MAIC analysis for Grade 1/2 diarrhoea, and Grade 3/4 major haemorrhage, infections, and atrial fibrillation. Given the lack of available head-to-head safety data, and the uncertainty associated with the MAIC analysis of safety outcomes, it may be more appropriate to exclude adverse event costs from the cost-minimisation analysis.

- The submission argued that the treatment durations for acalabrutinib and ibrutinib are expected to be similar, such that cost-minimisation will hold, regardless of the time on treatment. No evidence was provided to support this claim for the 17p deletion population.

6.85 The ESC and PBAC considered that the cost minimisation analysis with ibrutinib should include the combination therapy of acalabrutinib + obinutuzumab as this was the treatment most likely to be used in patients with 17p deletion.

Drug cost/patient/year

6.86 The estimated drug cost for acalabrutinib was $[redacted] per patient per year (based on 13.04 scripts using the requested effective DPMQ $[redacted] for 28 days treatment).

6.87 The estimated drug cost for obinutuzumab was $43,550 for a single six-month treatment course (based on 8 infusions using the weighted published public/private hospital (42%:58%) DPMA $5,443.78).

6.88 The estimated drug cost for chlorambucil was $1,604 for a single six-month treatment course (based on 12 scripts using the DPMQ $133.63 for 14 days treatment).

Estimated PBS usage & financial implications

6.89 This submission was not considered by DUSC. The submission used a mixed epidemiological/market share approach to estimate the utilisation and financial impacts associated with the PBS listing of acalabrutinib for use as monotherapy or in combination with obinutuzumab.

6.90 The sources of data used in the financial estimates are presented in the table below.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident CLL patients	Incidence of 6.7/100,000 (crude rate; 2015 AIHW estimate) applied to ABS Australian population projections (Series B 3222).	The submission assumed no growth in the incidence rate over time which may not be reasonable.
Probability of survival in CLL patients from diagnosis	The number of incident patients treated in the 9 years following diagnosis was estimated by applying CLL survival data to the incident patient numbers. Data on CLL survival by year after diagnosis was obtained from a Cancer Australia survival plot of survival (Figure B8(c) Cancer Australia, 2019).	Based on historic survival data (2007-2011). OS rates are likely to have improved with the availability of new treatments.
Proportion of first-line eligible patients who are unsuitable for a purine analogue	65%. Assumption based on feedback from Australian clinicians, treatment guidelines (Guidelines from the Croatian Cooperative Group for Haematologic Disease; Jaksic 2018); and an epidemiology modelling study (Jeyakumaran 2016).	The availability of a new oral treatment may result in increased uptake. Current NCCN treatment guidelines list acalabrutinib monotherapy and acalabrutinib + obinutuzumab as first-line therapies (regardless of age or comorbidities) in preference to fludarabine + cyclophosphamide + rituximab.
Proportion treated in year of diagnosis	33.3%. Assumption based on Australian clinician advice.	Unclear if reflective of Australian clinical practice.
Proportion of CLL patients requiring	50%. Assumption based on Australian clinician advice. The remaining 16.7% of patients who initiate treatment were assumed to be spread	The assumption that only 50% of patients would be treated over a lifetime was not adequately justified. The results from Dighiero 1998 were based on a

Parameter	Value applied and source	Comment
treatment over a lifetime	evenly over the following nine years (1.85% per year). The submission argued that this is consistent with an analysis of long-term data from two chlorambucil clinical trials, which showed that after 11 years of follow-up, 49% of patients did not require treatment (Dighiero 1998).	follow-up of 11 years, and may not be representative of lifetime treatment rates.
Proportion of eligible first-line patients treated with acalabrutinib + obinutuzumab	20%. Assumption. The submission argued that most patients would preferentially elect treatment with acalabrutinib monotherapy due to the safety profile of acalabrutinib monotherapy relative to acalabrutinib + obinutuzumab.	The proportion of patients who will be treated with acalabrutinib monotherapy and acalabrutinib + obinutuzumab is unclear, given similar efficacy results between acalabrutinib monotherapy and acalabrutinib + obinutuzumab, and the additional risk of adverse events with the addition of obinutuzumab. The ESC considered that the majority of patients without 17p deletion would be treated with acalabrutinib monotherapy, and the majority of patients with 17p deletion would be treated with acalabrutinib + obinutuzumab.
Proportion of patients remaining on treatment after initial treatment year.	Derived from time on treatment data sourced from the economic model: 2nd year: 83:0%; 3rd year: 72.9%; 4th year: 66.7%; 5th year: 61.7%; 6th year: 57.1%	Time on treatment in clinical practice may differ from the ELEVATE-TN trial.
Total dispensed chlorambucil + obinutuzumab scripts	3,750 scripts per year. Derived from PBS obinutuzumab dispensing data (PBS Items 10407R and 10418H) from September 2018 to August 2019.	During the evaluation it was noted that the 3,750 scripts were based on a 2-year period (Jan 2018 to Dec 2019) rather than Sep 2018 to Aug 2019 as reported in the submission. The actual underlying script count for 10407R and 10418H (Sep 2018 to Aug 2019) was 1,846 scripts.
Acalabrutinib price	$[redacted]. Requested effective DPMQ	-
Obinutuzumab price	$5,443.78; Weighted DPMA/DPMQ for Items 10407R and 10418H based on a Public (32.05%) and Private (67.95%) split.	The submission assumed the effective obinutuzumab price by applying a 30% discount to the obinutuzumab DPMQ/DMPA.
Chlorambucil + obinutuzumab price	$5,577.41. Derived from sum of the weighted obinutuzumab Public/Private DPMA/DPMQ and the chlorambucil DPMQ.	The submission assumed an effective chlorambucil + obinutuzumab price of $3,904.19 by applying a 30% discount to the total chlorambucil + obinutuzumab price.
Intravenous infusion of cytotoxic chemotherapy	$99.50. MBS item: 13918 (Administration of cytotoxic chemotherapy by intravenous infusion of more than 1 hours duration but not more than 6 hours duration).	Applied to each obinutuzumab infusion.

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; CLL = chronic lymphocytic leukaemia; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; ESC = Economic Sub-Committee; MBS = Medicare Benefits Schedule; NCCN = National Comprehensive Cancer Network; OS = overall survival; PBS = Pharmaceutical Benefits Scheme
Source: Table 4.1, pp171-173 of the submission.

6.91 Table 19 presents the estimated net cost to the PBS/RPBS of listing acalabrutinib for previously untreated CLL for patients who are unsuitable for treatment with a purine analogue.

Table 19: Financial impact of listing acalabrutinib for previously untreated patients

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Acalabrutinib + obinutuzumab scripts						
Total treated patients						
Total ACAL packs (13 per year)						
PBS/RPBS ACAL cost ($ per script)	$	$	$	$	$	$
Patient copayments ($14.89 per script)	$	$	$	$	$	$
Total cost of ACAL	$	$	$	$	$	$
Patients using OBI in combination with ACAL (20%)						
Total OBI scripts (8 per course)						
Total cost of OBI ($3,810.65 per script)[1]	$	$	$	$	$	$
Patient copayments ($14.89 per script)	$	$	$	$	$	$
Total cost of OBI	$	$	$	$	$	$
Total cost of listing ACAL + OBI	$	$	$	$	$	$
Displaced chlorambucil + obinutuzumab scripts						
Total dispensed OBI scripts[2]						
Proportion displaced by ACAL						
Total displaced OBI scripts						
PBS/RPBS CHL + OBI cost ($3,904.19 per script)[3]	-$	-$	-$	-$	-$	-$
Patient copayments ($14.89 per script)	$	$	$	$	$	$
Total cost of displaced CHL + OBI	-$	-$	-$	-$	- $	-$
Net cost to the PBS/RPBS						
Cost of listing ACAL + OBI	$	$	$	$	$	$
Displaced CHL + OBI cost	-$	-$	-$	-$	- $	-$
Net cost to PBS/RPBS	**$**	**$**	**$**	**$**	**$**	**$**
Net cost to PBS/RPBS (corrected)[2]	**$**	**$**	**$**	**$**	**$**	**$**
Net cost to MBS[4]	-$	-$	-$	-$	-$	-$
Net cost to Government	$	$	$	$	$	$
Net cost to Government (corrected)[2]	$	$	$	$	$	$

ACAL = acalabrutinib; CHL = chlorambucil; MBS = Medicare Benefits Schedule; OBI = obinutuzumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 4.9, pp181-182; Table 4.14, p.184; Table 4.15, p.185; Table 4.17, p.186; Table 4.25, pp188-189; Table 4.31, pp191-192; Table 4.36, p194; Table 4.37, p.195 of the submission.

1 Weighted price based on 32%/68% Public/Private split for obinutuzumab.

2 The annual number of displaced obinutuzumab scripts was erroneously based on 2 years of dispensing data for obinutuzumab rather than a single year. Based on a single year, the number of displaced scripts is per year. Additionally, a minor error in the '4a. Scripts Changed' Excel worksheet resulted in displaced script numbers of per year rather than the intended per year.

3 Submission assumed one chlorambucil script for every obinutuzumab script.

4 Net cost to Medicare calculated by multiplying the net obinutuzumab scripts by $99.50 (Medicare Item 13918).

The redacted table shows that at Year 6, the estimated number of total treated patients was 500 to < 5,000; total patients using OBI in combination with ACAL was < 500; total dispensed OBI scripts was 500 to < 5,000 and total displaced OBI scripts was 500 to < 5,000.

6.92 The estimated net cost to the PBS was $0 to < $10 million in Year 1 of listing, increasing to $100 million to < $200 million in Year 6, an estimated net cost of $300 million to < $400 million over the first six years of listing. The estimated net cost to Government was $0 to < $10 million in Year 1 of listing, increasing to $100 million to <$200 million in Year 6, an estimated net cost of $308.1 million over the first six years of listing.

6.93 The utilisation/financial estimates were considered to be uncertain due to the following issues:

- There were limited available data to inform the assumptions used to derive the number of treated patients. In particular, the assumption that only 50% of patients would be treated over a lifetime was not adequately justified. There is potential for additional growth in the number of treated patients (i.e. higher uptake among watch and wait patients) due to the availability of an effective, and more convenient oral therapy. The ESC noted the cost-effectiveness of acalabrutinib in a broader patient population has not been demonstrated.
- There is potential for use outside of the proposed restriction among patients who are suitable for treatment with a purine analogue. The NCCN treatment guidelines preference acalabrutinib monotherapy and acalabrutinib + obinutuzumab ahead of fludarabine + cyclophosphamide + rituximab for previously untreated CLL/SLL. The ESC noted the cost-effectiveness of acalabrutinib as an alternative to treatment with a purine analogue has not been demonstrated.
- Due to the immaturity of the ELEVATE-TN clinical data, the relative proportion of patients who will be treated with acalabrutinib monotherapy and acalabrutinib + obinutuzumab is unclear. The ESC considered that the majority of patients without the 17p deletion would receive treatment with acalabrutinib monotherapy and that for patients with the 17p deletion, the majority would receive combination therapy of acalabrutinib + obinutuzumab as, per the proposed restriction, these patients are likely to be younger and fitter, and they require a greater depth of response.
- The submission assumed no growth in the number of obinutuzumab scripts from 2019/2020 levels, which may not be reasonable. Additionally, the annual number of displaced scripts was erroneously based on 2 years of dispensing data for obinutuzumab rather than a single year.
- The duration of treatment for acalabrutinib ± obinutuzumab was estimated from time on treatment data extrapolated from the ELEVATE-TN trial. However, it is unclear whether the assumed treatment durations will reflect the time on treatment in clinical practice.
- The assumed uptake rates for acalabrutinib ± obinutuzumab in Years 4 to 6 of listing (100%) may not be realised.

Quality Use of Medicines

6.94 No quality use of medicines issues were identified in the submission, and no activities to support the quality use of medicines were proposed.

Financial Management – Risk Sharing Arrangements

6.95 The submission stated that the sponsor has proposed a risk sharing arrangement capping government expenditure on acalabrutinib to [redacted] cycles of therapy (approximately [redacted] years of therapy). The submission claimed that this cap was derived based on a mean treatment duration of 7 years from the ELEVATE-TN trial that equated to a maximum treatment duration of 8.9 years. The calculation of mean and maximum durations was not adequately documented in the submission and these values could not be validated during the evaluation.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of acalabrutinib, for use as monotherapy or in combination with obinutuzumab, for the first-line treatment of patients with CLL or SLL who are considered unsuitable for treatment with a purine analogue. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was unacceptably high and uncertain at the proposed price. The PBAC did not recommend the listing of acalabrutinib, for use as monotherapy or in combination with obinutuzumab, for the first-line treatment of patients with CLL or SLL who harbour a 17p deletion as non-inferiority versus ibrutinib was not adequately demonstrated.

7.2 The PBAC noted that the comments from consumers and from the Leukaemia Foundation, Lymphoma Australia and Rare Cancers Australia were all in support of the requested listing for acalabrutinib ± obinutuzumab, describing the need for treatment options in CLL patients unable to tolerate the current standard of care.

7.3 The PBAC considered the role and likely use of acalabrutinib in combination with obinutuzumab versus acalabrutinib monotherapy was unclear. The PBAC noted that although a post hoc analysis of the pivotal clinical trial (ELEVATE-TN) demonstrated that acalabrutinib + obinutuzumab was superior to acalabrutinib monotherapy on the basis of independent review committee-assessed progression free survival (HR = 0.49 [95% CI: 0.26, 0.95]), combination therapy was associated with substantial additional toxicity. Overall the Committee considered it likely that acalabrutinib monotherapy would be used in the majority of patients unsuitable for treatment with a purine analogue given the additional toxicity of combination therapy together with the general frailty of the patient population. However, the PBAC considered the submission's estimate of monotherapy use in 80% of patients was highly uncertain, and the patient population in which combination therapy would be used was inadequately defined. The PBAC considered it likely that combination therapy would be used in most patients with 17p deletion as the proposed restriction does not limit

use in such patients to those who are older than 65 years of age or to those with comorbidities.

7.4 For patients unsuitable for treatment with a purine analogue, the PBAC noted that comparisons were presented for acalabrutinib monotherapy and acalabrutinib + obinutuzumab versus the primary comparator, chlorambucil + obinutuzumab. Supplementary comparisons were also presented versus venetoclax + obinutuzumab. The PBAC considered that these comparisons were appropriate.

7.5 For the comparisons versus chlorambucil + obinutuzumab, the submission presented data from the ELEVATE-TN trial, which was a randomised, open-label trial which directly compared acalabrutinib monotherapy and acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab. For the analysis presented the median duration of follow up was 28 months.

7.6 The PBAC noted that both acalabrutinib monotherapy (HR = 0.20 [95% CI: 0.13, 0.30]) and acalabrutinib + obinutuzumab (HR = 0.10 [95% CI: 0.06, 0.17]) 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. Median progression free survival was not reached in either of the acalabrutinib treatment arms, with only 26 (15%) patients in the acalabrutinib monotherapy arm and 14 (8%) patients in the acalabrutinib + obinutuzumab arm experiencing a progression event.

7.7 The PBAC noted that there were no statistically significant differences in overall survival. The PBAC noted that the overall survival results were impacted by patients in the chlorambucil + obinutuzumab arm crossing over to receive acalabrutinib monotherapy after progression; however, considered that this reflected current clinical practice with the availability of treatments, including ibrutinib, for patients with relapsed or refractory disease.

7.8 In terms of safety versus chlorambucil + obinutuzumab, the PBAC 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. Overall, the PBAC 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 noted that both acalabrutinib monotherapy and acalabrutinib + obinutuzumab were associated with a higher incidence of serious adverse events compared to chlorambucil + obinutuzumab.

7.9 The PBAC considered that the efficacy and safety matching adjusted indirect comparisons (MAICs) between both acalabrutinib monotherapy and acalabrutinib + obinutuzumab and venetoclax + obinutuzumab were highly uncertain. The PBAC noted the heterogeneity between the ELEVATE-TN and CLL-14 trials which resulted in poor overlap between the trial populations and small effective sample sizes for the MAICs, and considered that it was unclear whether all relevant prognostic and effect

modifier variables had been identified. In addition, the PBAC noted that although there were no statistically significant differences, no non-inferiority margins had been proposed and the confidence intervals were wide. Overall, the PBAC considered that the efficacy and safety clinical claims based on the MAICs could not be supported.

7.10 The submission presented cost utility analyses comparing (i) acalabrutinib monotherapy with chlorambucil + obinutuzumab and (ii) acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab. The PBAC considered that the cost effectiveness of acalabrutinib monotherapy and acalabrutinib + obinutuzumab was difficult to ascertain due to uncertainties including:

- the 20 year time horizon. Noting that patients entered the model at 70 years of age, the PBAC considered that the proportions of acalabrutinib monotherapy and acalabrutinib + obinutuzumab patients alive at 20 years (approximately 25% and 30% respectively) were high. 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;
- that the model generated improvements in overall survival for patients in the acalabrutinib ± obinutuzumab 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;
- that 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 RR setting;
- that the mortality rates for the different lines of treatment lacked face validity;
- that 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; and
- the implausible 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).

7.11 The PBAC noted that the alternate base case presented in the ESC advice addressed some of the above issues (overall survival benefit for first line treatment, benefits and costs for the second-line treatments and the utility values). The PBAC considered that the resulting ICERs were high and, noting the large variability in the sensitivity analyses, highly uncertain.

7.12 In terms of the utilisation estimates, the PBAC considered that the incident patient population was uncertain due to the reasons outlined in paragraph 6.93, and noted that the utilisation increased substantially each year due to the high proportion of patients (57%) assumed to remain on treatment for at least 6 years. 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, and in patients previously untreated or treated later in their disease course.

7.13 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. The PBAC considered that this was not appropriate as acalabrutinib + obinutuzumab was likely to be used in most 17p deletion patients.

7.14 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. The PBAC noted the heterogeneity between the trials which resulted in poor overlap between the trial populations and small effective sample sizes for the MAICs, and considered that it was unclear whether all relevant prognostic and effect modifier variables had been identified. In addition, the PBAC noted that although there were no statistically significant differences, no non-inferiority margins had been proposed and the confidence intervals were wide. Overall the PBAC considered that the clinical claims describing acalabrutinib monotherapy as non-inferior in terms of effectiveness and superior in terms of safety compared to ibrutinib were not adequately supported.

7.15 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.

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

Outcome:
Rejected

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.