

6.10 ZANUBRUTINIB, Capsule 80 mg, Brukinsa[®], Beigene Aus Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required listing for zanubrutinib for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) considered unsuitable for treatment or retreatment with a purine analogue.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus ibrutinib.

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

Component	Description
Population	Patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) considered unsuitable for treatment or retreatment with a purine analogue
Intervention	Oral zanubrutinib 160 mg twice daily or 320 mg once daily until disease progression or unacceptable toxicity
Comparator	Oral ibrutinib 420 mg daily until disease progression or unacceptable toxicity Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity
Outcomes	Progression-free survival; overall response rate; time to next treatment; overall survival; safety
Clinical claim	In patients with relapsed or refractory CLL or SLL considered unsuitable for treatment or retreatment with a purine analogue, zanubrutinib is non-inferior to ibrutinib in terms of efficacy and safety. Zanubrutinib is non-inferior to acalabrutinib in terms of efficacy and safety

Source: Table 1-1, p14 of the submission

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC parallel process. An application seeking extension to the currently approved indications for zanubrutinib to include the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) was submitted to the TGA on 30 March 2022.
- 2.2 At the time of evaluation for PBAC consideration, the Round 1 Clinical Evaluation Report was available, as well as the sponsor's response to the report. The TGA delegate's overview was received in January 2023. The ACM considered that the product has an overall positive benefit-risk profile for the indication: 'BRUKINSA is indicated as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).'

Previous PBAC consideration

- 2.3 Zanubrutinib is listed on the PBS as a treatment for mantle cell lymphoma and Waldenström’s macroglobulinaemia.
- 2.4 A concurrent submission for zanubrutinib for the treatment of patients with previously untreated CLL/SLL, who are considered unsuitable for treatment with fludarabine-based chemoimmunotherapy, was considered at this same meeting (see published March 2023 PBAC meeting agenda).
- 2.5 Acalabrutinib (recommended at the March 2020 PBAC meeting); venetoclax (recommended at the November 2018 PBAC meeting); and ibrutinib (recommended subsequent to the November 2016 PBAC meeting) are currently listed on the PBS for patients with relapsed or refractory CLL/SLL considered unsuitable for treatment or retreatment with a purine analogue.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib, 80 mg capsule, 120	\$8,794.57 \$[SPA] ^a	1	120	5	Brukinsa
Category / Program: General Schedule					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Episodicity: Relapsed or refractory					
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Indication: Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Initial treatment					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					
AND					
Clinical criteria:					
The condition must have relapsed or be refractory to at least one prior therapy					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 0 or 1					
AND					
Clinical criteria:					
Patient must not have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must not have received treatment with another Bruton’s tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease); OR					
Patient must have developed intolerance to another Bruton’s tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory CLL/SLL					
AND					

Public Summary Document – March 2023 PBAC Meeting

Clinical criteria:
Patient must be considered unsuitable for treatment or retreatment with a purine analogue
Prescribing Instructions:
A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:
a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles;
b) Age is 70 years or older;
c) Age is 65 years or older 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, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;
d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;
e) Evidence of one or more 17p chromosomal deletions demonstrated by a Medicare Benefits Schedule listed test.
Treatment phase: Continuing treatment
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
Treatment phase: Grandfathering treatment
Clinical criteria:
Patient must have previously received non-PBS-subsidised treatment with this drug for relapsed or refractory CLL/SLL prior to 1 Month 2023 [insert listing date here]
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
The condition must have relapsed or be refractory to at least one prior therapy prior to initiating non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have a WHO performance status of 0 or 1 prior to initiating non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must be considered unsuitable for treatment or retreatment with a purine analogue prior to initiating non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:

Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease) prior to initiating non-PBS subsidised treatment with this drug for this condition; OR
Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory CLL/SLL prior to initiating non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must be considered unsuitable for treatment or retreatment with a purine analogue
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition

^a A special pricing arrangement is known to apply for the nominated comparator which will apply to zanubrutinib.

- 3.1 The submission noted that ibrutinib is subject to a special pricing arrangement and requested a special pricing arrangement to match the ibrutinib effective price.
- 3.2 The requested initial and continuing restrictions are consistent with the existing listings for ibrutinib and acalabrutinib for the treatment of relapsed or refractory CLL/SLL. This includes a criterion permitting use of zanubrutinib among patients who have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal. There is currently limited available clinical evidence assessing treatment outcomes among patients with BTK inhibitor intolerance who are subsequently treated with zanubrutinib; prior treatment with any BTK inhibitor was an exclusion criterion in the ALPINE trial. The ESC considered it may also be appropriate to allow patients to be retreated with a BTKi if it is preceded by a gap of 12- or 24-months post first-line treatment. The ESC considered that retreatment with a BTKi should only be permitted under the PBS once (i.e., whether the same agent or another BTKi). The ESC acknowledged that there were no firm data regarding a time-frame for a recurrence-free period after which it would be appropriate to retreat with an agent from the same class, or the clinical outcomes with retreatment.
- 3.3 The proposed criteria specifying suitability for treatment/retreatment with a purine analogue are identical to the criteria included in the restrictions for ibrutinib and acalabrutinib. However, the proposed population is narrower than the population in the ALPINE trial, which did not exclude patients based on purine analogue suitability. Given the expert advice from the clinical consultation on 1 December 2022 (as outlined in paragraph 4.7), the ESC considered it would be appropriate to remove the criteria that a patient must be unsuitable for treatment/retreatment with a purine analogue. The Pre-Sub-Committee Response (PSCR) and pre-PBAC response stated that the sponsor accepted expanding the proposed restriction so that zanubrutinib would not be restricted to patients considered unsuitable for treatment or retreatment with a purine analogue. The pre-PBAC response suggested that approximately 27-35% of patients may meet the current criteria for treatment or retreatment with a purine analogue, and subsequently may access BTKi treatment. The PBAC considered that the use of fludarabine-based chemoimmunotherapy in CLL

is low and declining and as such, there would be no increase in use associated with the restriction change.

- 3.4 The submission stated that the sponsor intends to commence a compassionate access program in January 2023, which would result in an estimated 50 patients requiring transitioning to PBS-subsidised supply (i.e., ‘grandfather’ arrangements). The Secretariat advised that the restriction could be simplified to a single restriction, with care taken so as to not inadvertently exclude such ‘grandfather’ patients.

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

4 Population and disease

- 4.1 CLL is characterised by the progressive accumulation of functionally incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, spleen, and liver. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating, and unintentional weight loss.
- 4.2 CLL is more common in men than women (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). SLL, another type of B-cell malignancy, is recognised as the same pathological entity as CLL, with a different clinical presentation. 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. The prognosis and aetiology of CLL and SLL are similar; therefore, the existing approaches to management, as well as treatment considerations are consistent with one another.
- 4.3 Characteristics associated with a worse prognosis include genetic factors (del17p/TP53 mutation, del11q, unmutated IGHV), biochemical/cell surface markers (serum thymidine kinase, serum β 2 microglobulin), and patient characteristics (male sex, older age, worse ECOG performance score). Deletion of the short arm of chromosome 17 (del17p) 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. Despite the effectiveness of first-line treatments in delaying disease progression, in most cases the clinical course of the CLL is characterised by consecutive episodes of disease progression and need for subsequent lines of therapy (Moreno 2020). The choice of therapy depends on several factors, including age, comorbidities, and the presence of prognostic genetic mutations.

- 4.5 Zanubrutinib is a potent, specific, and irreversible Bruton's tyrosine kinase (BTK) inhibitor. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Through BTK inhibition, zanubrutinib overcomes the B-cell antigen receptor and chemokine-controlled retention of malignant B-cells in their supportive microenvironments, thereby disrupting the pathogenesis of several B-cell malignancies such as CLL and SLL.
- 4.6 The submission positioned zanubrutinib as an alternative to treatment with other BTK inhibitors (ibrutinib or acalabrutinib) or venetoclax + rituximab for patients who are unsuitable for treatment/retreatment with a purine analogue. This broadly aligns with the most recent NCCN guidelines, although eligibility for treatment is no longer defined using suitability for a purine analogue; rather, the guidelines define suitable patients using a combination of age and comorbidity criteria (i.e., patients aged ≥ 65 years; and patients aged < 65 years with significant comorbidities or high-risk factors).
- 4.7 The pre-PBAC response noted that retreatment with a BTKi or B-cell lymphoma-2 inhibitor (BCL-2i) was a topic of discussion at the clinical consultation meeting held in December 2022 and stated that the sponsor was open to clinician and PBAC advice on the proportion of patients that would be retreated, as the reasons for wanting to use sequential BTKi therapy could vary.

5 Comparator

- 5.1 The submission nominated ibrutinib monotherapy as the main comparator. The main arguments provided in support of this nomination included that ibrutinib is a pharmacological analogue of zanubrutinib (a BTK inhibitor), which is currently PBS-listed for the treatment of patients with relapsed/refractory CLL/SLL who are unsuitable for treatment with a purine analogue. Ibrutinib is currently the most commonly used treatment in the relapsed/refractory CLL setting based on an analysis of PBS usage statistics provided by the sponsor. Ibrutinib is an appropriate main comparator.
- 5.2 Acalabrutinib is another pharmacological BTK inhibitor analogue that is PBS listed for relapsed/refractory CLL/SLL. The submission nominated acalabrutinib as a supplementary comparator. The PBAC considered that this was appropriate.
- 5.3 Other PBS listed treatments used in the relapsed/refractory setting, but which were not considered as relevant comparators, include:
- Venetoclax plus rituximab. Given the different mechanism of action for this treatment, it is expected that zanubrutinib would be less likely to replace this treatment in practice compared to the BTK inhibitors. The ESC considered zanubrutinib would be unlikely to replace venetoclax, with zanubrutinib being used in patients previously treated with venetoclax in the treatment naïve setting, or it would potentially displace venetoclax to a later line therapy.

- Idelalisib plus rituximab is also PBS-listed in an overlapping population, however, is not widely used in the second line setting due to lower efficacy and higher toxicity. The PBAC previously determined this is not an appropriate comparator in this indication (paragraph 7.5 acalabrutinib Public Summary Document (PSD), March 2020 PBAC meeting).
- 5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. In this case, the alternative therapies include acalabrutinib and ibrutinib.

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 (1), health care professionals (3), and from the three organisations, Haematology Society of Australia and New Zealand, Rare Cancers Australia, and Lymphoma Australia via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with zanubrutinib including fewer side effects, avoidance of hospitalisations and day care admissions, the opportunity for good quality of life and long-lasting remissions.

Clinical trials

- 6.3 The submission was based on a head-to-head comparison of zanubrutinib versus ibrutinib in relapsed/refractory CLL/SLL (ALPINE).
- 6.4 An indirect comparison and anchored matching adjusted indirect comparison (MAIC) of zanubrutinib (ALPINE) versus acalabrutinib (ELEVATE-RR; Byrd et al., 2021) via common reference ibrutinib was included as a supplementary analysis.
- 6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Zanubrutinib versus ibrutinib		
ALPINE NCT03734016	A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Hillmen P, Brown JR, Eichhorst BF et al. ALPINE: zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma.	July 2022 Future Oncol 2020; 16(10): 517-523
	Brown JR, Eichhorst BF, Hillmen P et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. ^a	NEJM 2022: DOI: 10.1056/NEJMoa2211582
Acalabrutinib versus ibrutinib		
ELEVATE-RR	Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial.	J Clin Oncol 2021; 39(31): 3441-3452

Source: Table 2-3, p39; Table 2-4, p40 of the submission.

^aPublished subsequent to lodgement of the zanubrutinib submission; identified during the evaluation.

6.6 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Zanubrutinib versus ibrutinib					
ALPINE	652	Phase 3, R, OL (median duration of follow-up approx. 25 months)	Unclear	Relapsed/refractory CLL/SLL	Overall response rate, progression-free survival, duration of response, time to treatment failure, overall survival, patient-reported outcomes, adverse events
Acalabrutinib versus ibrutinib					
ELEVATE-RR	533	Phase 3, R, OL (median duration of follow-up approx. 41 months)	Unclear	Relapsed/refractory CLL	Overall response rate, progression-free survival, overall survival, adverse events

Source: Table 2-8, p50; Table 2-9, p51; Table 2-10, p52; Table 2-11, p53; Table 2-12, p54; Table 2-16, p57; Table 2-21, p103 of the submission.

Abbreviation: CLL, chronic lymphocytic leukaemia; OL, open label; R, randomised; SLL, small lymphocytic lymphoma.

6.7 The ALPINE and ELEVATE-RR 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. However, each trial also included blinded assessments by an independent review committee. Assessments by the independent review committee were considered to be at a lower risk of bias.

6.8 The submission noted that there is no widely accepted minimal clinically important difference for progression-free survival, overall survival, or time to next treatment in this disease area.

6.9 The submission noted that previous PBAC submissions for CLL/SLL treatments have not nominated specific criteria for non-inferiority and, given the small sample sizes of trials in the CLL setting, it can be difficult to conclusively establish non-inferiority,

particularly in the absence of head-to-head data. No formal non-inferiority margin was applied in the submission for progression-free survival.

Comparative effectiveness

Head-to-head comparison of zanubrutinib versus ibrutinib

The result for the primary and secondary outcomes of the ALPINE trial, overall response rate by investigator assessment and independent central review respectively, are summarised in 6.10 Table 4 below.

Table 4: Overall response rate per investigator assessment and independent review committee (ITT analysis set); ALPINE

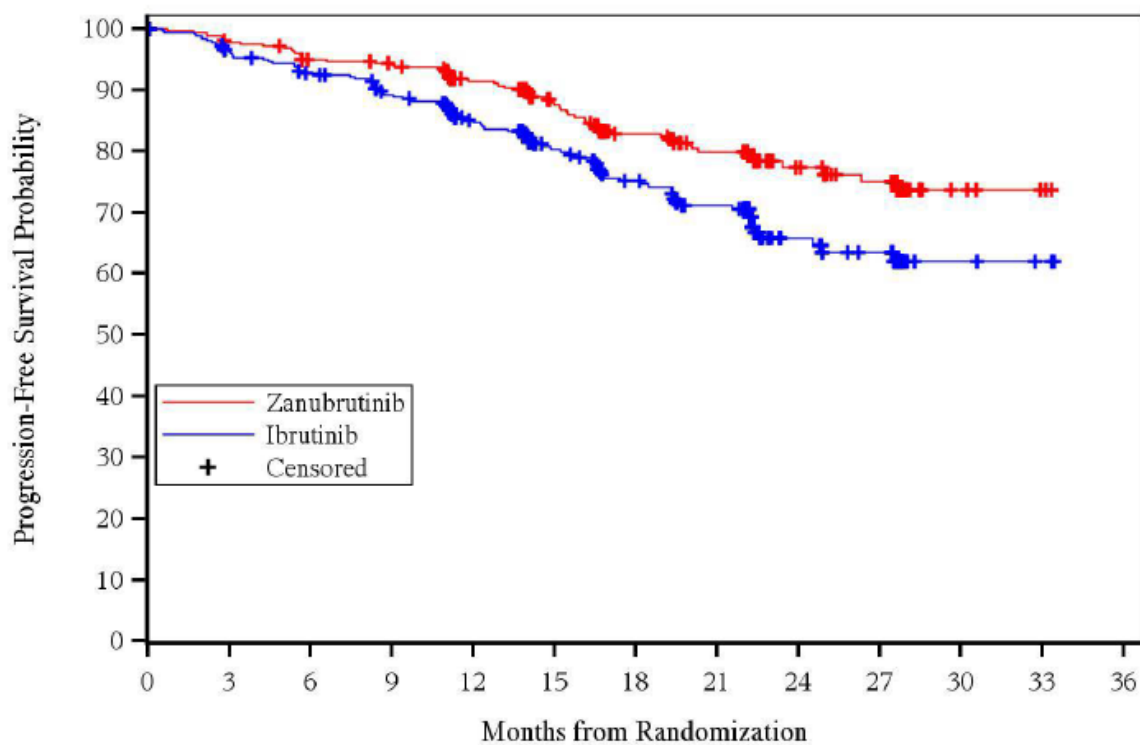
	Zanubrutinib n/N (%)	Ibrutinib n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Overall response rate by investigator assessment	260/327 (79.5)	231/325 (71.1)	1.12 (1.02, 1.22)*	8.4 (1.6, 15.2)
Overall response rate by independent central review	263/327 (80.4)	237/325 (72.9)	1.10 (1.01, 1.20)*	7.5 (1.04, 13.97)

Source: Table 2-19, p63; Table 2-20, p65 of the submission

* Noninferiority 1-sided p-value = <0.0001

- 6.11 The overall response rate by investigator assessment was statistically significantly higher for patients in the zanubrutinib arm (79.5% [95% CI: 74.7% to 83.8%]) compared with the ibrutinib arm (71.1% [95% CI: 65.8% to 75.9%]). The submission noted that because non-inferiority and superiority had already been met at the previous interim analysis, p-values for the current analysis are stated to be provided for descriptive purposes only. The interim analysis was not provided with the submission. Results for overall response rate assessed by independent central review were generally consistent with the investigator-assessed overall response rate.
- 6.12 Figure 1 presents the Kaplan-Meier plot of independent review committee-assessed progression-free survival for the ALPINE trial.

Figure 1: Kaplan-Meier plot of independent central review-assessed progression-free survival results for the ALPINE trial (ITT analysis set)



No. of Subjects at Risk

Zanubrutinib	327	314	301	297	263	209	174	158	71	61	5	2	0
Ibrutinib	325	304	290	272	228	181	151	133	58	47	4	2	0

Source: Figure 2-9, p67 of the submission

6.13 Table 5 summarises the results for progression-free survival for the ALPINE trial.

Table 5: Progression-free survival results for the ALPINE trial

	Zanubrutinib (N=327)	Ibrutinib (N=325)
Median duration of follow-up, months (range)	22.1 (22.1, 22.2)	22.1 (22.0, 22.2)
Independent central review-assessed		
Earliest event total, n (%)	60 (18.3)	87 (26.8)
- Progression, n	37 (11.3)	63 (19.4)
- Death, n	23 (7.0)	24 (7.4)
Median PFS, months (95% CI)	Not reached (NE, NE)	Not reached (NE, NE)
Within trial HR (95% CI)	0.61 (0.44, 0.86)	
KM estimate of PFS, % (95% CI)		
- 6 months	95.0 (92.0, 96.9)	92.8 (89.3, 95.1)
- 12 months	91.4 (87.8, 94.1)	84.7 (80.2, 88.3)
- 18 months	82.9 (77.8, 86.9)	75.1 (69.5, 79.9)
- 24 months	77.4 (71.2, 82.4)	65.8 (58.9, 71.9)
- 30 months	73.6 (66.2, 79.7)	62.0 (54.1, 68.9)
- 36 months	NE (NE, NE)	NE (NE, NE)
Investigator-assessed		
Earliest event total, n (%)	58 (17.7)	91 (28.0)
- Progression, n	34 (10.4)	63 (19.4)
- Death, n	24 (7.3)	28 (8.6)
Median PFS, months (95% CI)	Not reached (29.6, NE)	Not reached (NE, NE)
Within trial HR (95% CI)	0.55 (0.39, 0.76)	
KM estimate of PFS, % (95% CI)		
- 6 months	94.7 (91.6, 96.7)	93.4 (90.0, 95.6)
- 12 months	91.5 (87.8, 94.1)	84.5 (79.9, 88.1)
- 18 months	84.5 (79.7, 88.2)	74.6 (68.9, 79.4)
- 24 months	78.4 (72.3, 83.4)	63.6 (56.5, 69.8)
- 30 months	60.6 (29.5, 81.4)	60.9 (53.2, 67.8)
- 36 months	NE (NE, NE)	NE (NE, NE)

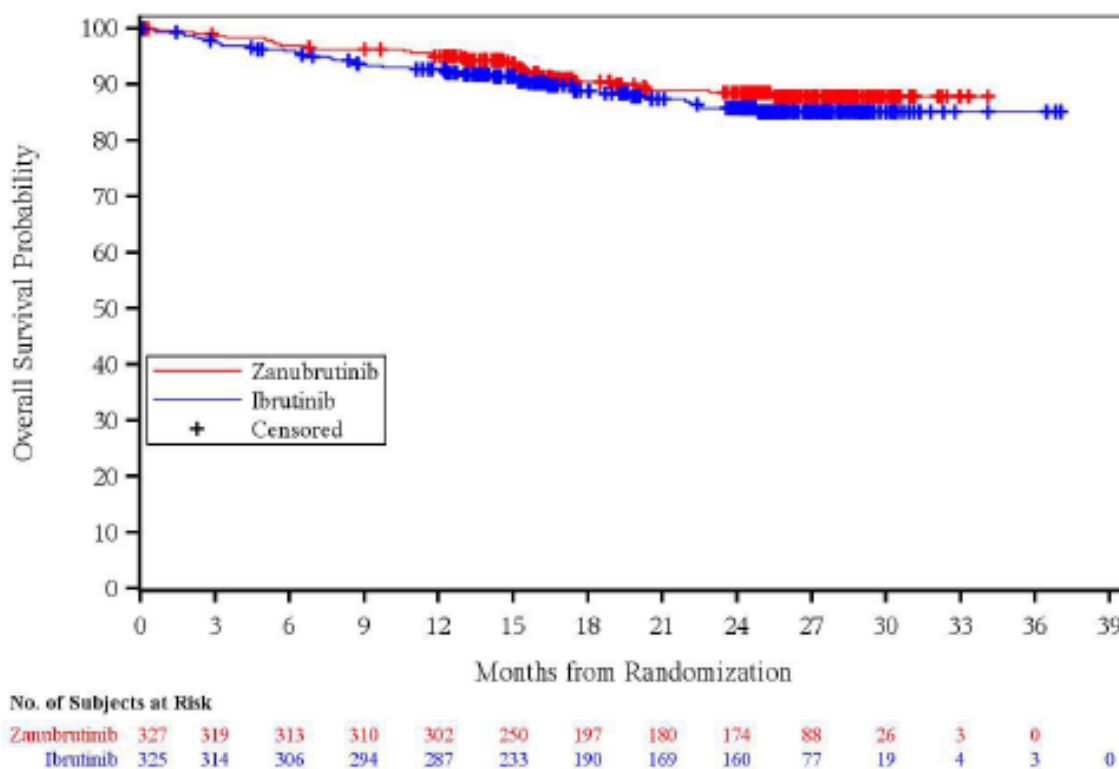
Source: Table 2-21, p66 of the submission; Table 14, p86; Table 15, p88 of the ALPINE clinical study report

6.14 As of the data cut-off (01 December 2021), the hazard ratio for progression-free survival assessed by independent central review was 0.61 (95% CI: 0.44 to 0.86) for the zanubrutinib arm compared with the ibrutinib arm. The 24-month event-free rate was 77.4% in the zanubrutinib arm and 65.8% in the ibrutinib arm. The submission noted that the final analysis of progression-free survival has been conducted and a press release reported that zanubrutinib achieved superior progression-free survival versus ibrutinib, as assessed by an independent central review committee and investigator, however the full results (beyond the information provided in the press release) were not available for inclusion in this submission at time of lodgement. During the evaluation, the results of the final analysis were published (Brown et al., 2022). These broadly agreed with results presented in the submission. Briefly, at a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to investigator-assessed progression-free survival among 652 patients (hazard ratio for disease progression or death, 0.65; 95% CI, 0.49 to 0.86). At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Among patients with del17p, a TP53 mutation, or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (hazard ratio for disease progression or

death, 0.53; 95% CI, 0.31 to 0.88). The percentage of patients with an overall response was higher in the zanubrutinib group than in the ibrutinib group. Treatment with zanubrutinib was associated with fewer adverse events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death, compared with ibrutinib. The PSCR stated that given this, the ability to switch BTK inhibitor treatments could be beneficial, particularly for patients experiencing cardiac events.

6.15 Figure 2 presents the Kaplan-Meier plot of overall survival for the ALPINE trial.

Figure 2: Kaplan-Meier plot of overall survival (ITT analysis set)



Source: Figure 2-12, p72 of the submission

6.16 Table 6 summarises the results for overall survival for the ALPINE trial.

Table 6: Overall survival (ITT analysis set); ALPINE

	Zanubrutinib N = 327	Ibrutinib N = 325
Follow up time, median months (95% CI)	24.9 (24.4, 25.5)	24.6 (24.2, 25.0)
Events, n (%)	33 (10.1)	40 (12.3)
Hazard ratio (95% CI)	0.80 (0.50, 1.28)	
Overall survival, median months (95% CI)	NE (NE, NE)	NE (NE, NE)
Event-free rate at, % (95% CI)		
- 6 months	96.9 (94.3, 98.3)	96.0 (93.2, 97.6)
- 12 months	95.0 (92.0, 96.9)	92.8 (89.4, 95.2)
- 18 months	90.5 (86.4, 93.3)	88.9 (84.7, 92.0)
- 24 months	88.5 (84.1, 91.8)	85.9 (81.0, 89.6)
- 30 months	87.8 (83.1, 91.3)	85.2 (80.2, 89.0)
- 36 months	NE (NE, NE)	(80.2, 89.0)

Source: Table 2-19, p63; Table 2-20, p65 of the submission; Table 19, p96 ALPINE clinical study report
Abbreviations: CI, confidence interval; NE, not estimable

- 6.17 As of the data cut-off date, there were 33 deaths reported in the zanubrutinib arm (10.1%) and 40 deaths reported in the ibrutinib arm (12.3%) in the ITT analysis set. Median overall survival was not reached in either arm with a median follow-up time of 24.9 months in the zanubrutinib arm and 24.6 months in the ibrutinib arm.
- 6.18 Results for patient-reported outcomes are summarised in Section 11.4.1.10, p98 of the ALPINE clinical study report. The estimated mean treatment difference in the patient-reported outcome endpoints showed generally similar health-related quality of life outcomes in the zanubrutinib-treated patients compared with the ibrutinib-treated patients in both the EORTC QLQ-C30 and the EQ-5D 5-Level.
- 6.19 Results of subgroup analyses for the outcome of overall response rate (both by independent central review, and investigator-assessed) are presented in the main body of the commentary. Results for the analysis of the overall response rate assessed by independent central review and investigator-assessed overall response rate were broadly consistent with one another; that is, most comparisons suggested no statistically significant difference between zanubrutinib and ibrutinib. No tests for treatment effect interaction were conducted. The ESC agreed this was consistent with the clinical claim of non-inferior efficacy.

Indirect comparison of zanubrutinib versus acalabrutinib

- 6.20 The submission presented Bucher method indirect comparisons for zanubrutinib (ALPINE) versus acalabrutinib (ELEVATE-RR) using the ibrutinib arm of each as the common reference. The submission noted a number of differences between these trials that may affect the transitivity assumption:
- ELEVATE-RR included more ‘high risk’ patients with del17p and/or del11q (45.1% and 62.3%, respectively), compared with the ALPINE trial (13.8% and 27.8%, respectively). ALPINE included patients after at least one prior line of treatment (median = 1 prior therapy). After a protocol amendment, the recruitment in ELEVATE-RR was limited to patients who had at least 2 prior lines of treatment (median=2 prior lines of therapy). However, some patients with only one prior line

of treatment had already been recruited and remained in the trial. Median follow-up in ALPINE was shorter than that in ELEVATE-RR. Immature data for long-term outcomes in ALPINE may lead to increased uncertainty in the relative efficacy estimates (e.g., HR for OS).

- ALPINE included patients with SLL (n=4% of zanubrutinib-treated patients), whereas ELEVATE-RR did not.
- Imbalances (>5% in proportions) between both active and control arms in ALPINE and ELEVATE-RR were also shown in terms of the following factors: unmutated IGHV, presence of complex karyotype, β 2-microglobulin, age, and presence of anaemia.

6.21 There were differences in the trial populations between ALPINE and ELEVATE-RR, suggesting that the indirect comparisons may not be appropriate. In particular, ELEVATE-RR recruited a ‘high risk’ population with cytogenetic mutations, who were at increased risk of disease progression compared with ALPINE.

6.22 The results for the indirect comparison between zanubrutinib versus acalabrutinib using ibrutinib treatment arms as a common reference for the outcome of independent central review committee-assessed progression-free survival, are summarised in Table 7.

Table 7: Bucher indirect comparison of independent central review committee-assessed progression-free survival for zanubrutinib versus acalabrutinib

Trial	Outcome	Zanubrutinib	Ibrutinib	Absolute difference	HR (95% CI)
ALPINE (22.1 months)	Progressed/dead n/N (%)	60/327 (18.3%)	87/325 (26.8%)	-8.5%	0.61 (0.44, 0.86)
	Median PFS, months (95% CI)	Not reached (NE)	Not reached (NE)	NE	-
Trial	Outcome	Acalabrutinib	Ibrutinib	Absolute difference	HR (95% CI)
ELEVATE-RR (38.4 months)	Progressed/dead n/N (%)	143/268 (53.4%)	136/265 (51.3%)	2.1%	1.00 (0.79, 1.27)
	Median PFS, months (95% CI)	38.4 (33.0, 38.6)	38.4 (33.0, 41.6)	0	-
Indirect comparison zanubrutinib (22.1 months) vs. acalabrutinib (38.4 months)					0.61 (0.40, 0.92)

Source: Table 2-36, p88 of the submission

Abbreviations: HR, hazard ratio; NE, not estimable; PFS, progression-free survival

6.23 Based on the results of the indirect comparison, treatment with zanubrutinib was associated with a longer duration of progression-free survival compared to acalabrutinib, a difference which was statistically significant (HR 0.61; 95% CI: 0.40, 0.92). The results should be interpreted with caution due to differences in trial populations and duration of follow-up.

6.24 The results for the indirect comparison between zanubrutinib versus acalabrutinib using ibrutinib treatment arms as a common reference for the outcome of overall survival, are summarised in Table 8.

Table 8: Bucher indirect comparison of overall survival for zanubrutinib versus acalabrutinib

Trial	Outcome	Zanubrutinib	Ibrutinib	Absolute difference	HR (95% CI)
ALPINE (24.9 months)	Events, n/N (%)	33/327 (10.1%)	40/325 (12.3%)	-2.2%	0.80 (0.50, 1.28)
	Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	NE	-
Trial	Outcome	Acalabrutinib	Ibrutinib	Absolute difference	HR (95% CI)
ELEVATE-RR (40.9 months)	Events, n/N (%)	63/268 (23.5%)	73/265 (27.5%)	-4.0%	0.82 (0.59, 1.15)
	Median OS, months (95% CI)	Not reached (NE)	Not reached (NE)	NE	
Indirect comparison zanubrutinib (24.9 months) vs. acalabrutinib (40.9 months)					0.98 (0.55, 1.74)

Source: Table 2-37, p89 of the submission

Abbreviations: HR, hazard ratio; NE, not estimable; PFS, progression-free survival

6.25 Based on the results of the indirect comparison, treatment with zanubrutinib was associated with a similar duration of overall survival compared to acalabrutinib (HR 0.98; 95% CI: 0.55, 1.74). The results should be interpreted with caution due to differences in trial populations and duration of follow-up. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals were wide.

Matching adjusted indirect comparisons of zanubrutinib versus acalabrutinib

6.26 The submission presented the results of an anchored MAIC comparing zanubrutinib with acalabrutinib based on individual patient data from the ALPINE trial and published results for the ELEVATE-RR trial. A technical report outlining the methodology used to conduct the MAIC was provided.

6.27 To match inclusion criteria for ELEVATE-RR (which recruited high-risk patients only [with del17p or del11q]), the ITT population in the ALPINE study was initially restricted to the subset of high-risk patients prior to matching. The ALPINE study originally randomised 327 and 325 patients in the zanubrutinib and ibrutinib arms, respectively; once restricted to high-risk patients, there were 128 and 123 patients in the zanubrutinib and ibrutinib arm, respectively. The significant numbers of lower-risk patients excluded from the ALPINE trial to conduct the MAIC suggests these trials may not be directly comparable.

6.28 An unadjusted comparison was conducted between the high-risk subset of ALPINE and the published treatment effect in ELEVATE-RR. The relative treatment effect on investigator-assessed PFS and IRC-assessed PFS was HR=0.66 (95% CI: 0.26, 1.68) and HR=0.75 (95% CI: 0.29, 1.95), respectively. The confidence intervals were wide, suggesting a high level of uncertainty in these estimates. Further, they are based on populations which remain unbalanced between ALPINE and ELEVATE-RR, and include a break in randomisation for patients included in ALPINE.

6.29 There were a number of variables which remained different between the two trials, even after lower risk patients were removed from ALPINE. In particular, there was an imbalance between the studies in terms of the proportion of patients with a TP53

mutation, varying combinations of cytogenic mutations (particularly del17p, no del11q, and mutated TP53), patients with at least 4 previous therapies, patients aged 75 years and over, and patients with an ECOG performance status scale score of 2. Although not reported in the submission, these may also indicate differences in the complement subgroups (for example, patients with 1, 2, or 3 prior therapies).

- 6.30 Weights for the anchored MAIC were derived after optimisation of the matching model in terms of effective sample size (ESS) and the included matching factors. Several sets of matching factors were investigated, starting from the full model including the entire set of available factors, followed by increasingly simplified models in terms of the included matching factors. Since the ELEVATE-RR study included CLL patients only, to preserve homogeneity in the ALPINE population SLL patients were also excluded from the analysis. Binet stage was used as the CLL staging variable, as it was defined in both studies. The matching model using all mutually available effect modifiers and prognostic factors with effect modifier potential resulted in an ESS of 29 and 25 in the zanubrutinib and ibrutinib arms, respectively. The small ESS suggested poor overlap between the trial populations. The resulting effective sample size was unlikely to be sufficient to reliably compare treatments.
- 6.31 To increase the ESS, a new model was fit excluding all prognostic factors regardless of effect modifier potential, and including only the effect modifiers considered to be most relevant, that is, IGHV mutation, cytogenetic mutation subgroups (del17p, del11q, and TP53 mutation status), β 2-microglobulin, number of prior lines, and Binet stage. This model resulted in an ESS of 71 and 62 in the zanubrutinib and ibrutinib arms, respectively, and is referred to as Model 1 (base case) in the submission. Anchored forms of population-adjusted indirect comparisons, where the evidence is connected by a common reference, rely on the assumption of ‘conditional constancy of relative effects’. This means that the relative treatment effects are assumed constant between studies at any given level of the effect modifiers, so there is no imbalance of unobserved effect modifiers between the 2 trial populations. Between-trial differences in the distribution of prognostic variables that are not effect modifiers do not affect inference, because the within-trial randomisation means that they should not impact on the relative treatment effects (assuming that the sample size is sufficiently large), however all known treatment effect modifiers should be adjusted for. Several potentially important variables, which were identified as prognostic factors with effect modifier potential, were either unavailable or not fit, including complex karyotype (≥ 3 abnormalities), bulky disease, age, sex, and relapsed/refractory status.
- 6.32 The submission also defined additional models designed to increase the ESS as sensitivity analyses. Model 2 was the same as Model 1 but excluded TP53 mutation as a matching factor. Model 3 was the same as Model 1 but excluded the number of lines of prior therapy as a matching factor. Model 2 resulted in an ESS of 77 each in the zanubrutinib and ibrutinib arms, whilst Model 3 resulted in an ESS of 84 and 63 in the zanubrutinib and ibrutinib arms, respectively. The ESS in all models was relatively low

compared with the initial sample size, but in the submission were considered to be sufficient for conducting an anchored MAIC.

- 6.33 Table 9 presents the proportion of patients with treatment effect modifier variables and prognostic factors chosen after matching using Model 1, in the ALPINE and ELEVATE-RR trials.

Table 9: Distribution of effect modifiers and prognostic variables after re-weighting of ALPINE for the MAIC of zanubrutinib and acalabrutinib (Model 1)

Effect modifier and prognostic characteristics, %	Active treatment arms		Control treatment arms	
	Acalabrutinib ELEVATE-RR (N = 268)	Re-weighted zanubrutinib ALPINE (ESS = 71)	Ibrutinib ELEVATE-RR (N = 265)	Re-weighted ibrutinib ALPINE (ESS = 62)
IGHV mutation (not mutated)	16.7	16.7	10.6	10.6
Del17p	45.3	45.3	45.3	45.3
Del11q	62.6	62.6	66.1	66.1
TP53 mutation	37.4	37.4	42.3	42.3
Complex karyotype (≥ 3 abnormalities)	46.3	45.4	47.2	62.8
β2-microglobulin (> 3.5 mg/L)	78.1	78.1	80.8	80.8
≥4 prior therapies	12.4	12.4	10.6	10.6
Bulky disease, Ldi ≥ 5 cm	47.8	52.0	51.3	56.6
Aged ≥ 75 years	16.4	26.2	16.2	24.3
Sex (male)	69.0	60.2	73.2	63.3
ECOG PS 2	7.5	2.1	8.3	5.7
Binet stage, A vs C	12.6	12.6	11.6	11.6
Binet stage, B vs C	45.3	45.3	42.6	42.6

Source: Table 20, p73 Attachment 3 MAIC Technical Appendix.

Abbreviations: del11q/del13q, deletion of the long arm of chromosome 11/13; del17p, deletion of the short arm of chromosome 17; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; IGHV, immunoglobulin heavy chain gene; Ldi, longest diameter; MAIC, matching adjusted indirect comparison.

Note: Variable names in **bold** text were those used for matching.

- 6.34 Post-matching characteristics for variables not chosen for matching were unbalanced after matching. 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.
- 6.35 Table 10 presents the results for the anchored MAIC of investigator-assessed and independent review committee-assessed progression-free survival based on a median follow-up of approximately 22.1 months for ALPINE, and approximately 38.4 months for ELEVATE-RR.

Table 10: Results for the MAIC of investigator-assessed and independent review committee-assessed progression free survival for zanubrutinib versus acalabrutinib

Model	HR (95% CI)
Investigator-assessed progression free survival	
Unadjusted high-risk population (N = 251) ^a	0.66 (0.26, 1.68)
MAIC adjusted: Model 1 (ESS = 133.5)	0.65 (0.20, 2.18)
MAIC adjusted: Model 2 (ESS = 154.9)	0.70 (0.22, 2.21)
MAIC adjusted: Model 3 (ESS = 147.2)	0.74 (0.23, 2.42)
Independent review committee-assessed progression free survival	
Unadjusted high-risk population (N = 251) ^a	0.75 (0.29, 1.95)
MAIC adjusted: Model 1 (ESS = 133.5)	0.67 (0.22, 2.04)
MAIC adjusted: Model 2 (ESS = 154.9)	0.90 (0.30, 2.66)
MAIC adjusted: Model 3 (ESS = 147.2)	0.80 (0.27, 2.42)

Source: Table 23, p81; Table 24, p87 Attachment 3 MAIC Technical Document.

Abbreviations: CI, confidence interval; ESS, effective sample size after reweighting; HR, hazard ratio; MAIC, matching adjusted indirect comparison.

^a The unadjusted comparison included only CLL patients with non-missing information for all selected matching factors

- 6.36 Prior to adjustment of the MAIC (i.e., based on an unadjusted comparison of high-risk patients from ALPINE [zanubrutinib] and patients from ELEVATE-RR [acalabrutinib]), the hazard ratio for progression-free survival favoured zanubrutinib but the difference was not statistically significant. After adjustment, the difference in progression-free survival between zanubrutinib and acalabrutinib remained not statistically significant in all the matching models. Overall, relative treatment effects generated via MAIC were estimated with large uncertainty. No non-inferiority margin was proposed in the submission.
- 6.37 The submission noted that, due to immaturity of overall survival data in the ALPINE population, MAIC results based on the latest data cut were considered as preliminary only, and results should be interpreted with caution. Table 11 presents the results for the anchored MAIC of overall survival based on a median follow-up of approximately 24.9 months for ALPINE, and approximately 40.9 months for ELEVATE-RR.

Table 11: Results for the MAIC of overall survival for zanubrutinib versus acalabrutinib

Model	HR (95% CI)
Unadjusted high-risk population (N = 251) ^a	0.76 (0.23, 2.46)
MAIC adjusted: Model 1 (ESS = 133.5)	0.41 (0.10, 1.65)
MAIC adjusted: Model 2 (ESS = 154.9)	0.51 (0.13, 1.97)
MAIC adjusted: Model 3 (ESS = 147.2)	0.46 (0.12, 1.73)

Source: Table 34, p117 Attachment 3 MAIC Technical Document.

Abbreviations: CI, confidence interval; ESS, effective sample size after matching; HR, hazard ratio; MAIC, matching adjusted indirect comparison.

^a The unadjusted comparison included only CLL patients with non-missing information for all selected matching factors

- 6.38 Prior to adjustment of the MAIC (i.e., based on an unadjusted comparison of the high-risk population from ALPINE [zanubrutinib] and ELEVATE-RR [acalabrutinib]), the hazard ratio for overall survival favoured zanubrutinib but the difference was not statistically significant (HR 0.76; 95% CI: 0.23, 2.46). After adjustment, the difference in overall survival between zanubrutinib and acalabrutinib remained not statistically significant in any of the matching models.

6.39 Overall, relative treatment effects for progression free survival and overall survival generated via MAIC were estimated with large uncertainty. The evaluation considered that the lack of a statistically significant difference may not be sufficient to establish non-inferiority, and the 95% confidence intervals are wide. Results should be interpreted with caution due to the low effective sample size in the ALPINE trial after matching, differences in the duration of follow-up between the trials, and differences between the trial populations that were not explicitly adjusted for in the MAIC, including age, sex, bulky disease, complex karyotype, and ECOG performance score. The ESC considered that, on balance, the results were sufficient to establish non-inferiority for PFS and OS of zanubrutinib with acalabrutinib.

Comparative harms

Head-to-head comparison of zanubrutinib versus ibrutinib

6.40 A summary of treatment-emergent adverse events in the ALPINE trial is presented in Table 12.

Table 12: Overall summary of treatment-emergent adverse events in ALPINE (safety analysis set)

	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients with at least one treatment-emergent adverse event	315 (97.2)	320 (98.8)
Grade 3 or above	192 (59.3)	211 (65.1)
Serious	104 (32.1)	141 (43.5)
Leading to death	24 (7.4)	29 (9.0)
Leading to treatment discontinuation	42 (13.0)	57 (17.6)
Leading to dose modification	143 (44.1)	181 (55.9)
- Leading to dose interruption	137 (42.3)	175 (54.0)
- Leading to dose reduction	34 (10.5)	49 (15.1)
Treatment-related	238 (73.5)	264 (81.5)
Treatment-related Grade 3 or above	104 (32.1)	128 (39.5)

Source: 2-29, p76 of the submission

6.41 Overall, the proportions of patients who experienced adverse events were comparable between the 2 arms. A lower proportion of patients in the zanubrutinib arm had Grade 3 or higher adverse events, serious adverse events, adverse events leading to death, adverse events leading to treatment discontinuation, adverse events leading to dose modification, and treatment-related adverse events compared with patients in the ibrutinib arm.

6.42 Specific adverse events with an incidence difference $\geq 5\%$ between the treatment arms included:

- Atrial fibrillation: zanubrutinib 4.0% versus ibrutinib 11.1%
- Diarrhoea: zanubrutinib 13.9% versus ibrutinib 21.9%
- Muscle spasms: zanubrutinib 2.8% versus ibrutinib 12.3%
- Upper respiratory tract infection: zanubrutinib 17.9% versus ibrutinib 12.7%.

- 6.43 The most common Grade 3 or above adverse events in the zanubrutinib arm and the ibrutinib arm, respectively, included:
- Neutropenia: 14.2% versus 13.9%
 - Hypertension: 12.7% versus 10.2%
 - Decreased neutrophil count: 4.3% versus 4.0%
 - COVID-19 pneumonia: 4.3% versus 3.1%
 - COVID-19: 4.0% versus 2.2%
 - Pneumonia: 4.0% versus 7.4%.
- 6.44 Treatment-related adverse events that occurred at an incidence difference of $\geq 5\%$ between the 2 arms were diarrhoea (7.4% in the zanubrutinib arm versus 13.6% in the ibrutinib arm), muscle spasms (0.9% versus 8.0%), and atrial fibrillation (2.2% versus 9.3%).
- 6.45 The incidence of adverse events of special interest by category was generally comparable between the zanubrutinib and ibrutinib arms, except for atrial fibrillation and flutter (4.6% in the zanubrutinib arm versus 12.0% in the ibrutinib arm). Other small differences between treatment arms were observed for: neutropenia (26.9% [zanubrutinib] versus 23.8% [ibrutinib]), infections Grade 3 or higher (18.5% versus 22.5%), and thrombocytopenia (11.1% versus 15.1%).

Naïve comparison of zanubrutinib versus acalabrutinib

- 6.46 The submission included a naïve comparison of adverse events between zanubrutinib and acalabrutinib, based on ALPINE and ELEVATE-RR. Given the different follow up periods of the trials, the submission stated that it would not be reasonable to draw any conclusions on comparative safety profiles based on the raw number of events in the two studies. However, as both studies were direct comparisons with ibrutinib it is possible to comment on a few key differences that likely exist between the adverse event profiles of these BTK inhibitors. Table 13 summarises the most commonly reported adverse events in either study that occurred with a more than 5% difference between the study's respective treatment arms.

Table 13: Naïve comparison between ALPINE and ELEVATE-RR for adverse events occurring in ≥10% (any grade) of patients in either treatment arm

	ALPINE		ELEVATE-RR	
	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)	Acalabrutinib (N = 266) n (%)	Ibrutinib (N = 263) n (%)
Patients with at least one treatment-emergent adverse event	315 (97.2)	320 (98.8)	NR	NR
Atrial fibrillation	13 (4.0)	36 (11.1)	24 (9.0)	41 (15.6)
Diarrhoea	45 (13.9)	71 (21.9)	92 (34.6)	121 (46.0)
Dyspepsia	17 (5.2)	21 (6.5)	10 (3.8)	32 (12.2)
Upper respiratory tract infection	58 (17.9)	41 (12.7)	71 (26.7)	65 (24.7)
Contusion	43 (13.3)	33 (10.2)	31 (11.7)	48 (18.3)
Muscle spasms	9 (2.8)	40 (12.3)	16 (6.0)	35 (13.3)
Back pain	16 (4.9)	19 (5.9)	20 (7.5)	34 (12.9)
Headache	25 (7.7)	30 (9.3)	92 (34.6)	53 (20.2)
Cough	32 (9.9)	26 (8.0)	77 (28.9)	56 (21.3)
Hypertension	59 (18.2)	56 (17.3)	23 (8.6)	60 (22.8)

Source: Table 2-43, p98 of the submission

Abbreviations: NR, not reported

6.47 Results were generally consistent with the known adverse event profile of BTK inhibitors. Acalabrutinib and zanubrutinib treatment appear to result in fewer events of atrial fibrillation, diarrhoea and muscle spasms compared with ibrutinib in the relapsed/refractory CLL population.

Benefits/harms

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

Clinical claim

6.49 The submission described zanubrutinib as non-inferior in terms of effectiveness and safety compared to ibrutinib. The evaluation and the ESC considered this was reasonable.

6.50 The PBAC considered that the clinical claims of non-inferior effectiveness and safety for zanubrutinib versus ibrutinib were reasonably supported by the data.

6.51 The submission described zanubrutinib as non-inferior in terms of effectiveness and safety compared to acalabrutinib. The ESC, while acknowledging there was a high level of uncertainty, supported the clinical claim that zanubrutinib is non-inferior to acalabrutinib.

6.52 The PBAC considered that the clinical claims of non-inferior effectiveness and safety for zanubrutinib versus acalabrutinib were reasonably supported by the data, but with a high level of uncertainty.

Economic analysis

6.53 The submission presented a cost-minimisation approach of zanubrutinib versus ibrutinib based on the claim of non-inferior effectiveness and safety.

- 6.54 The submission proposed the following equi-effective doses:
- Zanubrutinib 320 mg once daily or 160 mg twice daily is equi-effective to ibrutinib 420 mg once daily.
- 6.55 The equi-effective doses were based on the doses of zanubrutinib and ibrutinib used in the ALPINE trial. These doses were consistent with the doses recommended in the respective Product Information documents. For both zanubrutinib and ibrutinib, treatment is recommended to continue until disease progression or unacceptable toxicity.
- 6.56 The overall median treatment durations in ALPINE were 23.82 months in the zanubrutinib arm and 17.73 months in the ibrutinib arm at a follow-up time of 22.1 months. The submission acknowledged that the follow-up time of 22.1 months in the ALPINE trial is too short to derive true mean treatment durations for both treatments, but stated that it is expected the actual treatment duration of zanubrutinib would be equal to ibrutinib (and also acalabrutinib) in clinical practice. The cost-minimisation, based on equivalent costs of 30 days of treatment, assumed equivalent treatment duration. The PBAC previously considered that for the indication of relapsed/refractory CLL/SLL, the duration of treatment for acalabrutinib (in the cost minimisation approach) should equal that which was accepted for ibrutinib at the time of its PBS listing (paragraph 7.11, acalabrutinib PSD, March 2020 PBAC meeting).
- 6.57 Treatment costs of adverse events that occurred at an incidence difference of $\geq 5\%$ between the 2 arms in the ALPINE trial were included as a supplementary analysis to demonstrate potential cost savings associated with listing zanubrutinib to the healthcare system.
- 6.58 The submission noted that ibrutinib is subject to a special pricing arrangement and requested a special pricing arrangement to match the ibrutinib effective price. A cost minimisation based on the effective price of ibrutinib is presented in the Committee-in-Confidence section of the ESC advice.
- 6.59 Table 14 presents the derivation of the cost-minimised price for zanubrutinib based on the ibrutinib published price.

Table 14: Derivation of the cost-minimised price for zanubrutinib based on the ibrutinib published price

	Ibrutinib	Zanubrutinib
Proposed equi-effective dose	420 mg daily	320 mg once daily or 160 mg twice daily
Pack quantity (30 days treatment)	90	120
AEMP (published)	\$8,633.29	\$8,633.29

Source: Table 3-8, p113 of the submission

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

- 6.60 Based on the published price of ibrutinib, the cost-minimised DPMQ for zanubrutinib was \$8,794.57.
- 6.61 The submission estimated annual savings of \$53.79 per patient (\$4.42 per month) associated with the different adverse event profiles of zanubrutinib versus ibrutinib as a supplementary analysis. Given the uncertainty associated with adverse event rates

in clinical practice compared with the trial setting, the exclusion of adverse event costs from the base case cost-minimisation was appropriate.

- 6.62 Based on the evidence provided, the submission claimed that zanubrutinib is non-inferior in terms of effectiveness and safety compared to both ibrutinib and acalabrutinib. An economic evaluation comparing zanubrutinib with acalabrutinib was not presented and equi-effective doses were not provided in the submission. Based on recommended doses, the equi-effective doses would be zanubrutinib 320 mg once daily or 160 mg twice daily is equi-effective to acalabrutinib 100 mg twice daily, if non-inferiority is accepted.

Drug cost/patient/year

- 6.63 Based on published prices, the drug cost per patient per year for zanubrutinib is \$107,073.89 (based on the proposed published DPMQ of \$8,794.57 × 12.175 scripts per year).
- 6.64 The drug cost per patient per year for ibrutinib is \$107,073.89 (based on the published DPMQ of \$8,794.57 × 12.175 scripts per year).
- 6.65 Treatment adherence and persistence were not explicitly included in the cost minimisation or financial implications, as zanubrutinib was assumed to directly substitute for ibrutinib scripts.
- 6.66 The effective price of ibrutinib for relapsed/refractory CLL/SLL is unknown to the sponsor, however the submission noted that the sponsor would be willing to adopt the effective price for ibrutinib.

Estimated PBS usage & financial implications

- 6.67 This submission was not considered by DUSC. The submission used a market-share approach to estimate the utilisation and financial impacts associated with the PBS listing of zanubrutinib. The sources of data used in the financial estimates are presented in Table 15 below.

Table 15: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value applied and source	Comment
Current utilisation of therapies among patients with relapsed or refractory CLL/SLL	22,799 (all); 13,734 (ibrutinib). PBS statistics; Script data for ibrutinib, venetoclax, acalabrutinib, and idelalisib from June 2021 to July 2022.	PBS-listed chemoimmunotherapy combinations (such as chlorambucil plus rituximab) were not included in the analysis, which may not be reasonable.
Annual growth in relapsed or refractory CLL/SLL scripts	5.21% per year. Acalabrutinib relapsed/refractory CLL/SLL Public Summary Document, March 2020. Originally based on the AIHW 'Cancer in Australia 2014' report. Derived based on the mean annual growth in the 5-year CLL prevalence rate from 2009 (4,146) to 2012 (4,828).	The estimate of annual growth in the prevalence of CLL/SLL is relatively old and may not reflect current values, which may be higher than those proposed.
Ibrutinib CLL/SLL scripts per year	14,450 in Year 1, increasing to 18,627 in Year 6. Estimated current utilisation of 13,734 ibrutinib scripts per year extrapolated based on assumed annual growth in relapsed/refractory CLL/SLL scripts of 5.21%.	There may be potential for zanubrutinib to substitute for other therapies particularly acalabrutinib. The ESC noted there were 3,928 scripts dispensed for acalabrutinib from June 2021 to July 2022. ^a
Proportion of ibrutinib scripts displaced by zanubrutinib	5% in Year 1, increasing to 15% in Year 6. The acalabrutinib relapsed/refractory CLL/SLL Public Summary Document, March 2020 stated that the ESC considered that ibrutinib displacement was likely to be in the range of 10% to 30%; the current submission assumed an uptake rate half that.	The evaluation considered this was uncertain, as it is unclear whether clinicians would be more likely to initiate relapsed/refractory patients on zanubrutinib based on the claimed safety advantages and place in guidelines, or to use alternatives (acalabrutinib or ibrutinib) given the longer duration of clinical trial data and likely greater clinical experience. The PBAC considered that zanubrutinib would replace ibrutinib, rather than displace it.
Grandfathered patients	█ ¹ . Sponsor assumption, based on the number of patients expected to enter the sponsor's early access program.	The submission stated that the program is expected to commence in January 2023, therefore, grandfathered patients are likely to be included in the market share estimates of prevalent patients and may have been double counted in the submission. The PBAC considered the grandfathered patients would already be accounted for given the market share approach used.

Source: Table 4-2, p116; Table 4-4, p117; Table 4-6, p118; Table 4-7, p118; Table 4-8, p119 of the submission; 'Section 4 _RR' Excel workbook.

Abbreviations: CLL, chronic lymphocytic leukaemia; DPMQ, dispensed price for maximum quantity; SLL, small lymphocytic lymphoma

^a Worksheet 'CLL_scripts2021-22' of the submission's financial estimates spreadsheet (PBS item code 12117R).

The redacted values correspond to the following ranges:

¹ < 500

6.68 Table 16 presents the estimated financial implications to the PBS/RPBS of listing acalabrutinib, based on the cost-minimised price of zanubrutinib (DPMQ \$8,794.57) and the published price of ibrutinib (DPMQ \$8,794.57).

Table 16: Estimated use and financial impact of zanubrutinib to the PBS/RPBS (published price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total estimated ibrutinib scripts	7	7	7	7	7	7
Proportion of ibrutinib scripts displaced by zanubrutinib	5%	10%	10%	15%	15%	15%
PBS/RPBS scripts	1	1	1	1	1	1
PBS/RPBS scripts for 50 grandfathered patients	1	5	5	5	5	5
Total zanubrutinib scripts	1	1	1	1	1	1
PBS/RPBS cost	2	2	2	6	6	6
Patient copayments	3	3	3	3	3	3
Net PBS/RPBS cost	2	2	2	6	6	6
Reduction in cost of ibrutinib with listing of zanubrutinib						
Ibrutinib scripts replaced	1	1	1	1	1	1
PBS/RPBS cost	3	3	3	3	3	3
Patient copayments	4	4	4	4	4	4
Net PBS/RPBS cost	3	3	3	3	3	3
Net cost of listing zanubrutinib on the PBS						
Including grandfathered patients						
Total cost of zanubrutinib	2	2	2	6	6	6
Net savings from displaced ibrutinib	3	3	3	3	3	3
Net cost to PBS/RPBS	4	\$0 ⁴	4	4	4	4
Not including grandfathered patients						
Total cost of zanubrutinib	4	2	2	6	6	6
Net savings from displaced ibrutinib	3	3	3	3	3	3
Net cost to PBS/RPBS	4	4	4	4	4	4

Source: Source: Table 4-2, p116; Table 4-4, p117; Table 4-6, p118; Table 4-7, p118; Table 4-8, p119; Table 4-10, p120; Table 4-11, p121 of the submission; 'Section 4 _RR' Excel workbook.

Abbreviations: CLL, chronic lymphocytic leukaemia; DPMQ, dispensed price for maximum quantity; SLL, small lymphocytic lymphoma

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$10 million to < \$20 million

³ net cost saving

⁴ \$0 to < \$10 million

⁵ < 500

⁶ \$20 million to < \$30 million

⁷ 10,000 to < 20,000

6.69 The estimated net cost to the PBS/RPBS for zanubrutinib in relapsed/refractory CLL/SLL patients is \$10 million to < \$20 million in Year 1, with no costs in Years 2-6, a total of \$10 million to < \$20 million over the first 6 years of listing. The cost to the PBS/RPBS in Year 1 is due to grandfathered patients. When grandfathered patients are removed, assuming market share only, the result is cost neutral. Grandfathered patients are likely to already be included in the market share estimates.

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

- Treatment regimens, and the associated market share for medicines for CLL/SLL are rapidly changing, for example there is a concurrent submission for zanubrutinib that was considered in March 2023 for the first-line treatment of CLL/SLL. Use of BTK inhibitors in the first-line (treatment naive) setting is likely to result in a reduction in use of BTK inhibitors in the relapsed/refractory setting,

which will have flow-on effects to the estimates presented in the submission. If retreatment with a BTKi is permitted, the ESC considered that this may also impact utilisation.

- Zanubrutinib was assumed to substitute only for ibrutinib, and the submission used ibrutinib script numbers to estimate use of zanubrutinib, assuming an ibrutinib displacement rate of 5% in Year 1, increasing to 15% in Year 6. This was half the rate that the ESC had considered would be likely for acalabrutinib in relapsed/refractory CLL/SLL (paragraph 6.95, acalabrutinib PSD, March 2020). The PBAC considered that zanubrutinib would replace ibrutinib rather than displace it. The evaluation and the ESC considered that it would have been appropriate for both ibrutinib and acalabrutinib script numbers to be used to determine use of zanubrutinib, given that zanubrutinib may substitute for both ibrutinib and acalabrutinib. The ESC considered that patients currently treated with ibrutinib (or acalabrutinib) would be unlikely to switch to zanubrutinib, but new incident patients commencing a BTKi would likely receive either acalabrutinib or zanubrutinib (potentially in a 50%:50% ratio, depending on clinician preference), given the adverse event profile of ibrutinib. Due to the large pool of prevalent patients already being treated with ibrutinib or acalabrutinib, the ESC considered that utilisation of zanubrutinib in the R/R setting may be low initially before increasing. In the pre-PBAC response, the sponsor concurred with ESC, and noted that the relatively recent listing of acalabrutinib may have complicated any estimated market share adoption. The pre-PBAC response further considered that, based on the cost-minimisation approach adopted for the submission that an additional layer of assumptions would be unlikely to materially impact the financial estimates and overall cost to Government.
- The submission stated that there was minimal uncertainty in the estimates due to the CMA presented, and the market share approach to the financial estimates, and therefore, no inputs were tested in the sensitivity analysis. The evaluation stated the impact of listing zanubrutinib will be cost-neutral if it substitutes only for ibrutinib or acalabrutinib (which was previously cost-minimised against ibrutinib). However, if zanubrutinib substitutes for other listed medicines there may be additional costs associated with listing.

Financial Management – Risk Sharing Arrangements

- 6.71 In terms of the existing RSA, in its March 2020 consideration of acalabrutinib, ‘the PBAC noted that a two-tier RSA is in place for R/R CLL/SLL that encompasses both ibrutinib and venetoclax. The PBAC recommended that acalabrutinib join the current arrangement and considered that no changes to the subsidisation caps would be appropriate.’ (paragraph 7.13, acalabrutinib PSD, March 2020 PBAC Meeting).
- 6.72 The submission noted that the Department may wish to combine caps on zanubrutinib in the treatment naïve and relapsed/refractory settings to manage expenditure related to sequencing of BTKi/BCL-2i treatments. The submission proposed a

combined RSA across the treatment naïve and relapsed refractory settings, and noted that a combined cap may include the following:

- A weighted price for zanubrutinib across the treatment naïve and relapsed/refractory settings, with weightings based on prescription volume of BTK inhibitor/BCL-2i agents in each setting.
- Utilisation in the relapsed/refractory setting would be combined with utilisation in the treatment naïve setting based on the estimates provided in each financial model, and expenditure calculated based on the weighted price.
- Any use beyond the proposed annual subsidisation caps would result in the application of a 1% rebate.

- 6.73 The PSCR stated that there is a strong financial rationale for a combined RSA across the treatment naïve and relapsed and refractory CLL/SLL settings to manage uncertainty in uptake and erosion between the settings, and potentially lead to cost savings over the 5-year RSA Deed period. The pre-PBAC confirmed this was the preferred approach.
- 6.74 The submission acknowledged that, given the changing BTK inhibitor/BCL-2i landscape, agents from both BTKi and BCL-2i classes may join the combined RSA in future. If a shared RSA is recommended, it was noted that separate PBS item codes in the treatment naïve and relapsed/refractory indications would be required to enable easier utilisation tracking in each line of therapy at the expense of PBS readability.
- 6.75 The ESC noted that if there are separate PBS item codes for the two treatment indications, then separate SPAs could be applied, and a weighted price would not be required. The ESC further noted that, if recommended, it would be appropriate for zanubrutinib to join the current RSA in place for relapsed/refractory CLL/SLL so that the cost per patient in the relapsed/refractory indication for zanubrutinib is equivalent to that for the other therapies. The ESC noted that if zanubrutinib use in treatment naïve patients was to be included in the current RSA, then the subsidisation caps would need to be increased to account for this use.
- 6.76 The ESC noted an alternative approach would be for a single line agnostic listing for zanubrutinib (i.e., a listing for the ‘treatment of CLL/SLL’, but with a criterion with at least 2 parameters for: (i) treatment -naïve disease, (ii) relapsed/refractory disease). In this situation a weighted price for zanubrutinib across the two settings would be required, and the options would be for (i) zanubrutinib to have a separate RSA or (ii) zanubrutinib to join the RSA for in place for relapsed/refractory CLL/SLL. The ESC noted that if zanubrutinib does not join the current RSA, then price for zanubrutinib in relapsed/refractory disease should be based on the cost per patient that was considered cost-effective for ibrutinib at the time of its listing. For this scenario the ESC requested estimates of the weights for calculating a single price for use across both indications be provided in the pre-PBAC response.

- 6.77 The pre-PBAC response suggested that these weights should be based on the estimated use of zanubrutinib in treatment naïve disease compared to the estimated use for the entire BTKi therapies in relapsed/refractory disease. The weightings provided in the pre-PBAC response could not be replicated.

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

7 PBAC Outcome

- 7.1 The PBAC recommended extending the listing of zanubrutinib to include the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of zanubrutinib would be acceptable if it were cost-minimised to the least costly alternative of ibrutinib and acalabrutinib. The PBAC noted that in order for the cost per patient for zanubrutinib in relapsed/refractory disease to be equivalent to that for the alternative therapies it would be appropriate for zanubrutinib to join the current RSA in place for relapsed/refractory CLL/SLL.
- 7.2 The PBAC noted the input from individuals, health professionals and organisations. The PBAC noted the consumer comments described a range of benefits of treatment with zanubrutinib including fewer side effects, avoidance of hospitalisations and day care admissions, the opportunity for good quality of life and long-lasting remissions.
- 7.3 The PBAC noted that zanubrutinib had also been recommended at the March 2023 PBAC meeting for treatment naïve CLL/SLL. The PBAC recalled that in relation to that consideration, that consumer comments received had detailed the difficulty of the 'watch and wait' approach for asymptomatic patients. The PBAC recalled that it had considered that to restrict the potential for use where the consensus is to 'watch and wait', that it would be appropriate to include the International Workshop on CLL (iwCLL) criteria for commencing treatment (latest version, which was Hallek 2018 at the time of PBAC consideration) in the restriction for zanubrutinib, and to flow this change onto the restrictions for all treatments for CLL/SLL in both the treatment naïve and the relapsed/refractory indications. The PBAC confirmed that this change should be flowed-on to zanubrutinib in relapsed/refractory CLL/SLL disease.
- 7.4 The PBAC noted that the restrictions for ibrutinib, acalabrutinib, and venetoclax plus rituximab in relapsed/refractory CLL/SLL disease require patients to be inappropriate for a purine analogue. The PBAC recalled that based on advice received at the clinical consultation on 1 December 2022, that it had considered that the requirement for patients to be considered unsuitable for treatment or retreatment with a purine analogue should be removed from the restrictions for all PBS listed drugs for CLL/SLL in the relapsed or refractory setting. The PBAC further considered that this change should be flowed on to zanubrutinib.
- 7.5 The PBAC considered that the requirement for patients to have a WHO performance status of 0 or 1 was not crucial, and that this requirement could be removed from the

requested restriction. The PBAC further considered that this change should be flowed on to other therapies for CLL/SLL.

- 7.6 The PBAC considered that it would not be appropriate to allow patients to be retreated with a Bruton's tyrosine kinase inhibitor (BTKi) for relapsed/refractory disease if they progressed with the same drug at any stage of the disease. The PBAC considered, consistent with the PBS BTKi listings in the relapsed/refractory setting, it would be appropriate to allow patients who develop intolerance to zanubrutinib of a severity necessitating permanent treatment withdrawal to be treated with an alternative BTKi.
- 7.7 The concurrent submission for zanubrutinib monotherapy for the treatment of treatment naive CLL/SLL was also recommended at the March 2023 PBAC meeting. The PBAC noted advice from the Department that separate PBS item codes for treatment naïve disease and relapsed/refractory disease would allow easier administration of any RSA caps.
- 7.8 The PBAC considered that submission's nomination of ibrutinib as the main comparator was appropriate. The PBAC noted that acalabrutinib was appropriately nominated as a supplementary comparator.
- 7.9 The PBAC noted that the submission was based on a head-to-head comparison of zanubrutinib versus ibrutinib in relapsed/refractory CLL/SLL (ALPINE), and that an indirect comparison and anchored matching-adjusted indirect comparison (MAIC) of zanubrutinib (ALPINE) versus acalabrutinib (ELEVATE-RR) was also presented as a supplementary analysis via the common reference of ibrutinib.
- 7.10 The PBAC noted that based on a median treatment duration of 23.82 months for patients in the zanubrutinib arm and 17.73 months for patients in the ibrutinib arm, with a follow-up time of 22.1 months in the ALPINE trial, the overall response rate by investigator assessment was statistically significantly higher for patients in the zanubrutinib arm compared with the ibrutinib arm, that progression free survival (PFS) was numerically higher for zanubrutinib than ibrutinib, there was no difference in overall survival, and that health-related quality of life was similar.
- 7.11 The PBAC noted that treatment emergent adverse events (TEAEs) of Grade 3 or above, serious TEAEs, and treatment-related adverse events, were numerically lower in patients treated with zanubrutinib compared to ibrutinib.
- 7.12 The PBAC noted the transitivity issues associated with the Bucher method indirect treatment comparison of zanubrutinib to acalabrutinib, that the MAIC was based on individual patient data from the ALPINE trial and published data from the ELEVATE-RR trial, that selected high risk patients only were selected from the ALPINE trial and that there was no statistically significant difference in PFS between zanubrutinib and acalabrutinib in the matching models. The PBAC noted that while there was a large degree of uncertainty based on these issues, that ESC had considered the evidence sufficient to establish non-inferiority of zanubrutinib compared to acalabrutinib for

the outcomes of PFS and overall survival.

- 7.13 The PBAC noted that the adverse events of atrial fibrillation, diarrhoea and muscle spasms appeared to be lower in patients treated with both zanubrutinib and acalabrutinib than in patients treated with ibrutinib.
- 7.14 The PBAC considered that the clinical claims of non-inferior effectiveness and safety of zanubrutinib versus ibrutinib were reasonably supported by the data.
- 7.15 The PBAC considered that the clinical claims of non-inferior effectiveness and safety for zanubrutinib versus acalabrutinib were reasonably supported by the data, but with a high level of uncertainty.
- 7.16 The PBAC noted that the submission had presented a cost-minimisation approach (CMA) of zanubrutinib to ibrutinib with the proposed equi-effective doses of zanubrutinib 320 mg once daily (or 160 mg twice daily) = ibrutinib 420 mg once daily, that since follow-up in the trial was insufficient to derive true mean treatment durations the CMA was based on equivalent durations of treatment, and that the cost of treating adverse events had been excluded from the CMA. The PBAC noted that the sponsor had agreed to match the effective price for ibrutinib.
- 7.17 The PBAC considered that the submission's approach to the CMA and the proposed equi-effective doses were appropriate.
- 7.18 The PBAC noted equi-effective doses for zanubrutinib and acalabrutinib were not provided in the submission. The PBAC considered it would be reasonable to use the recommended doses (zanubrutinib 320 mg once daily or 160 mg twice daily and acalabrutinib 100 mg twice daily) and based on the CMA as outlined in paragraph 7.16, the cost of zanubrutinib should be no more than for acalabrutinib.
- 7.19 The PBAC noted that the submission had used a market share approach to derive the expected utilisation and the cost to the PBS/RPBS over 6 years and considered that this was appropriate. The PBAC noted that the submission had assumed that zanubrutinib would replace 5% of ibrutinib scripts in Year 1 of listing, increasing to replacement of 15% of ibrutinib scripts in Year 6, but considered this estimate to be uncertain. The PBAC noted the submission had estimated script numbers for ibrutinib for the treatment of relapsed and refractory CLL/SLL and assumed that current utilisation would grow by 5.21% per year. However, the PBAC considered that based on the acalabrutinib script numbers in 2021 versus 2020 that growth in script numbers could be higher at 7.9%, and therefore that zanubrutinib script numbers could be higher than estimated. The PBAC considered that zanubrutinib would also substitute for acalabrutinib, and on that basis, that script numbers for zanubrutinib might also be higher than estimated.
- 7.20 The PBAC noted that zanubrutinib for treatment naïve CLL/SLL was recommended at this same meeting and considered that use of zanubrutinib in treatment naïve disease would likely reduce use of BTK inhibitors, including zanubrutinib, in relapsed/refractory disease.

- 7.21 The PBAC noted that the financial estimates assumed that approximately 50 patients would be grandfathered from the sponsor’s compassionate access program, and that zanubrutinib was not expected to grow the market. The PBAC considered the grandfathered patients would already be accounted for given the market share approach used and should not be accounted for separately.
- 7.22 The PBAC noted that in the pre-PBAC response it was estimated that patient numbers, and therefore script numbers would increase by approximately 30% due to the removal of the requirement for patients to be ‘inappropriate for fludarabine-based chemoimmunotherapy’. However, the PBAC considered that the use of fludarabine-based chemoimmunotherapy in CLL is low and declining and as such, there would be no increase in use associated with the restriction change.
- 7.23 In terms of the estimated financial impact, the PBAC considered that as zanubrutinib would substitute for ibrutinib and acalabrutinib, and given listing is on a cost-minimisation basis, there would be no additional cost to the PBS/RPBS.
- 7.24 The PBAC noted that in order for the cost per patient for zanubrutinib in relapsed/refractory disease to be equivalent to that for the alternative therapies it would be appropriate for zanubrutinib to join the current RSA in place for relapsed/refractory CLL/SLL.
- 7.25 The PBAC noted that flow-on restriction changes would be required for other therapies for CLL/SLL to ensure the therapies are only prescribed in accordance with the iwCLL guidance (latest version) in relation to when to prescribe drug treatment for this condition/when to monitor the patient without therapy.
- 7.26 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because zanubrutinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ibrutinib or acalabrutinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.27 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add indication as follows:

Public Summary Document – March 2023 PBAC Meeting

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib 80 mg capsule, 120	NEW 2 MP	1	120	5	Brukinsa
Safety Net Rule Penalty Applies? Yes					
Restriction Summary / Treatment of Concept: Authority Required (to share identical restriction summary number with ibrutinib and acalabrutinib)					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Treatment of relapsed/refractory disease					
Clinical criteria:					
The condition must have relapsed or be refractory to at least one prior therapy					
AND					
Clinical criteria:					
The treatment must only be prescribed for patients with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.					
Treatment criteria:					
Patient must not be undergoing retreatment with this drug where prior, active treatment of CLL/SLL with this same drug was unable to prevent disease progression					
AND					
Treatment criteria:					
Patient must be undergoing treatment through this treatment phase listing for the first time; or					
Patient must be undergoing treatment through this treatment phase listing on a subsequent occasion, with disease progression being absent					
Administrative advice:					
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative advice: No increase in the maximum number of repeats may be authorised.					
Administrative advice: Special Pricing Arrangements apply.					
Administrative advice:					
The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy – see ‘Indications for treatment’ section; and (2) recognising progressive disease – see ‘Definition of response, relapse, and refractory disease’ section.					
See the following literature reference for details:					

Public Summary Document – March 2023 PBAC Meeting

Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. <i>Blood</i> vol. 131, 25 (2018): 2745-2760.

Flow-on changes to be implemented concurrently with the zanubrutinib changes

8.2 Amend the following venetoclax listings as follows:

Category / Program: General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
venetoclax 10 mg tablet [14] (&) venetoclax 50 mg tablet [7] (&) venetoclax 100 mg tablet [7] (&) venetoclax 100 mg tablet [14], 1 pack	11630D MP	1	1	0	Venclexta
Edit Restriction Summary / ToC: Authority Required					
Indication: Chronic lymphocytic leukaemia (CLL)					
Treatment Phase: Initial treatment – Dose titration occurring at the start of treatment for relapsed/refractory disease					
Clinical criteria: Patient must not have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria: Patient must be considered unsuitable for treatment or retreatment with a purine analogue					
AND					
Clinical criteria: The condition must have relapsed or be refractory to at least one prior therapy					
AND					
Clinical criteria: Patient must have a WHO performance status of 0 or 1					
AND					
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition					
AND					
Clinical criteria: The treatment must only be prescribed for patients with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition					
AND					
Clinical criteria: The treatment must be used as monotherapy for this condition under this restriction					
Treatment criteria: Patient must not be undergoing retreatment with this drug where prior, active treatment of CLL/SLL with this same drug was unable to prevent disease progression					
Prescribing Instructions:					

Public Summary Document – March 2023 PBAC Meeting

	<p>A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:</p> <p>a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles;</p> <p>b) Age is 70 years or older;</p> <p>c) Age is 65 years or older 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, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;</p> <p>d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;</p> <p>e) Evidence of one or more 17p chromosomal deletions demonstrated by a Medicare Benefits Schedule listed test.</p>
	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>Administrative advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy – see 'Indications for treatment' section; and (2) recognising progressive disease – see 'Definition of response, relapse, and refractory disease' section.</p> <p>See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.</p>

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
medicinal product pack					
VENETOCLAX					
venetoclax 100 mg tablet, 120	11639N MP	1	120	5	Venclexta
Restriction Summary / Treatment of Concept: Authority Required *****UNCHANGED*****					
	Indication: Chronic lymphocytic leukaemia (CLL)				
	Treatment Phase: Continuing treatment				
	Clinical criteria:				
	Patient must have previously received PBS-subsidised treatment with this drug for this condition				
	AND				
	Clinical criteria:				
	The treatment must be in combination with rituximab for up to a maximum of 6 cycles, followed by monotherapy				

Public Summary Document – March 2023 PBAC Meeting

	AND
	Clinical criteria:
	The treatment must be ceased on disease progression or on completion of 24 months of PBS-subsidised treatment under this restriction with this drug for this condition, whichever comes first
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

8.3 Amend the following ibrutinib listings as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
medicinal product pack					
IBRUTINIB					
ibrutinib 140 mg capsule, 90	11213E MP	1	90	5	Imbruvica
Edit Restriction Summary / ToC: Authority Required (to share identical restriction summary number as zanubrutinib and acalabrutinib)					
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy – see ‘Indications for treatment’ section; and (2) recognising progressive disease – see ‘Definition of response, relapse, and refractory disease’ section. See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. <i>Blood</i> vol. 131, 25 (2018): 2745-2760.				
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Treatment Phase: Initial treatment Treatment of relapsed/refractory disease				
	Clinical criteria:				
	The treatment must be the sole PBS-subsidised therapy for this condition				
	AND				
	Clinical criteria:				
	The condition must have relapsed or be refractory to at least one prior therapy				

Public Summary Document – March 2023 PBAC Meeting

	AND
	Clinical criteria:
	Patient must have a WHO performance status of 0 or 1
	AND
	Clinical criteria:
	<i>The treatment must only be prescribed for patients with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition</i>
	AND
	Clinical criteria:
	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease); or
	Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory CLL/SLL
	AND
	Clinical criteria:
	Patient must be considered unsuitable for treatment or retreatment with a purine analogue
	AND
	Clinical criteria:
	<i>The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.</i>
	Treatment criteria:
	<i>Patient must not be undergoing retreatment with this drug where prior, active treatment of CLL/SLL with this same drug was unable to prevent disease progression</i>
	AND
	Treatment criteria:
	<i>Patient must be undergoing treatment through this treatment phase listing for the first time; or</i>
	<i>Patient must be undergoing treatment through this treatment phase listing on a subsequent occasion, with disease progression being absent</i>
	Prescribing Instructions: A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following: a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles; b) Age is 70 years or older; c) Age is 65 years or older 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, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen; d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia; e) Evidence of one or more 17p chromosomal deletions demonstrated by a Medicare Benefits Schedule listed test.
Remove Restriction Summary / ToC: Authority Required	
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Continuing treatment

Public Summary Document – March 2023 PBAC Meeting

	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

8.4 Amend the following acalabrutinib listings as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ACALABRUTINIB					
acalabrutinib 100 mg capsule, 56	12117R MP	1	56	5	Calquence
Edit Restriction Summary / ToC: Authority Required (to share identical restriction summary number with to ibrutinib and zanubrutinib)					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Administrative advice: <i>The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are:</i> (1) when to treat versus when to monitor the patient without therapy – see ‘Indications for treatment’ section; and (2) recognising progressive disease – see ‘Definition of response, relapse, and refractory disease’ section. <i>See the following literature reference for details:</i> <i>Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.</i>				
	Indication: Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Treatment Phase: Initial treatment – Treatment of relapsed/refractory disease				
	Clinical criteria:				
	The treatment must be the sole PBS-subsidised therapy for this condition				
	AND				
	Clinical criteria:				
	The condition must have relapsed or be refractory to at least one prior therapy				
	AND				
	Clinical criteria:				

Public Summary Document – March 2023 PBAC Meeting

	Patient must have a WHO performance status of 1 or less
	AND
	Clinical criteria:
	<i>The treatment must only be prescribed for patients with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition</i>
	AND
	Clinical criteria:
	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must be considered unsuitable for treatment or retreatment with a purine analogue
	AND
	Clinical criteria:
	Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of CLL/SLL (untreated or relapsed/refractory disease); or
	Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory CLL/SLL
	AND
	Clinical criteria:
	<i>The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.</i>
	Treatment criteria:
	<i>Patient must not be undergoing retreatment with this drug where prior, active treatment of CLL/SLL with this same drug was unable to prevent disease progression</i>
	AND
	Treatment criteria:
	<i>Patient must be undergoing treatment through this treatment phase listing for the first time; or</i>
	<i>Patient must be undergoing treatment through this treatment phase listing on a subsequent occasion, with disease progression being absent</i>
	Prescribing Instructions: A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following: a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles; b) Age is 70 years or older; c) Age is 65 years or older 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, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen; d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia; e) Evidence of one or more 17p chromosomal deletions demonstrated by a Medicare Benefits Schedule listed test.
Remove Restriction Summary / ToC:: Authority Required	
	Indication: Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Continuing treatment of relapsed or refractory CLL/SLL

	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

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

9 Context for Decision

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

10 Sponsor’s Comment

The sponsor had no comment.