Zanubrutinib (Brukinsa®) as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL)

General information

Drug description [1]	Indication [2]
Zanubrutinib (Brukinsa®) is a next-generation, selective Bruton tyrosine kinase (BTK-) inhibitor.	Zanubrutinib (Brukinsa®) as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).

Current treatment [3]

- NICE recommends the following first line treatment options for CLL/small lymphocytic leukaemia (SLL):
  - Acalabrutinib monotherapy
  - Venetoclax with obinutuzumab
  - Venetoclax monotherapy
  - Ibrutinib monotherapy
  - Idelalisib monotherapy
  - Idelalisib with rituximab
  - Obinutuzumab with chlorambucil
  - Bendamustine monotherapy
  - Rituximab with fludarabine and cyclophosphamide

Regulatory status

EMA [2, 4]

Approval status for this indication: On 13 October 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Brukinsa®.

The CHMP adopted a new indication:

- Brukinsa® as monotherapy is indicated for the treatment of adult patients with CLL.

Other indications:

- Brukinsa® as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.
- Brukinsa® as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.

✓ **Medicine under additional monitoring**

FDA [5, 6]

Approval status for this indication: On 19 January 2023, the FDA approved zanubrutinib (Brukinsa®) for CLL or small lymphocytic lymphoma (SLL).

Other indications: Brukinsa® is indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (indication approved under accelerated approval based on overall response rate).
- WM
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen (indication is approved under accelerated approval based on overall response rate).

Costs

120 Brukinsa® hard capsules 80 mg = € 4,936.57 (ex-factory price) [7].

Warnings and precautions [4, 5]

- **Haemorrhage**
  - Monitor for bleeding and manage appropriately.
- **Infections**
  - Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed.

- **Cytopenias**
  - Monitor complete blood counts during treatment.
- **Second primary malignancies**
  - Other malignancies have occurred in patients including skin cancers and non-skin carcinomas. Monitor and advise patients to use sun protection.
- **Cardiac arrhythmias**
  - Monitor for signs and symptoms of arrhythmias and manage appropriately.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise women of the potential risk to a foetus and touse effective contraception.
- **Tumour lysis syndrome**
  - Tumour lysis syndrome has been infrequently reported with zanubrutinib therapy, particularly in patients who were treated for CLL. Assess relevant risks (e.g., high tumour burden or blood uric acid level) and take appropriate precautions. Monitor patients closely and treat as appropriate.
- **Brukinsa® contains sodium**
  - This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Study characteristics: SEQUOIA trial [1, 8, 9]

Trial name	*n*	Intervention (I), group A	Comparator (C), group B	Group C[1], n=111	PE	Characteristics	Biomarker	Funding	Publication(s)
SEQUOIA, BGB-3111-304 NCT03336333	590 (1:1)	oral zanubrutinib at 160 mg twice per day in 28-day cycles until disease progression or unacceptable toxicity	6 cycles of IV bendamustine (90 mg/m² of BSA on days 1 and 2 of each cycle) plus rituximab (375 mg/m² of BSA on the day before or day of the start of cycle 1, and 500 mg/m² of BSA on day 1 of cycles 2 to 6)[2]	oral zanubrutinib at 160 mg twice per day in 28-day	PFS by independent review committee	**ongoing**[3], multicentre, open-label, randomised, phase 3 study	-	BeiGene	[1]

Efficacy	Safety
Prespecified interim analysis (group A vs. group B) was done on 27 July 2021: median follow-up of 26.2 months (IQR 23.7-29.6) **Patient who had progressed or died**: 15% vs. 30% **Median PFS**: not reached in either group (group A 95% CI, NE-NE; group B 28.1 months-NE; HR 0.42, 95% CI 0.28-0.63; two-sided p<0.0001) **Estimated PFS at 24 months**: 85.5% (95% CI, 80.1-89.6) vs. 69.5% (95% CI, 62.4-75.5) **Patients who have progressed or died by data cut-off (by investigator assessment):** 12% vs. 24%; HR 0.42, 95% CI 0.27-0.66; two-sided p=0.00011	**Group A vs. group B:** **Infections grade ≥3**: n=39/240 (16%) vs. 240/227 (19%) **Serious AEs**: n=88/240 (37%) vs. n=113/227 (50%) **Any-grade atrial fibrillation**: n=8/240 (3%) vs. 6/227 (3%) **Major bleeding events**: n=12/240 (5%) vs. n=4/227 (2%)

[1] Patients with del(17)(p13.1) were not randomly assigned because chemoimmunotherapy was not considered a suitable option based on international guidelines; these patients were assigned to cohort 2, received zanubrutinib (group C), and were analysed separately.
[2] Control group patients with centrally confirmed disease progression could **cross over** to receive zanubrutinib.
[3] The SEQUOIA trial is currently ongoing; estimated study completion date is 10/2024.

ORR (by independent review committee): 94.6% (95% CI, 91.0–97.1) vs. 85.3% (95% CI, 80.1–89.6) **Complete response (by independent review committee):** 7% vs. 15% **ORR (by investigator):** 97.5% (95% CI, 94.7–99.1) vs. 88.7% (95% CI 83.9-92.4) **Complete response (by investigator):** 9% vs. 18% I**nvestigator-assessed progression due to Richter transformation (post-hoc analysis):** 2% vs. <1% **Median duration of response (by independent review committee and investigator):** NR (95% CI, NE–NE for both types of assessment) vs. 30.6 months (95% CI for independent review committee, 25.5–NE; 95% CI for investigator assessment, 26.2–NE) **Patient who had died at data cut-off:** 7% and 6% **Median OS**: NR in either group (95% CI group A NE–NE, group B 30.6–NE) **Estimated 24-month OS**: 94.3% (95% CI, 90.4–96.7) vs. 94.6% (95% CI, 90.6–96.9) No significant **difference in OS** was observed between groups A and B (HR 1.07, 95% CI, 0.51–2.22; p=0.87) **Patient-reported outcomes**: not yet available **Updated analysis for group C:** (at a median follow-up of 30.5 months; IQR 27.6–33.1) 14% of patients had **progressed or died** per independent review committee; one patient had died without progression, with the median PFS by independent review committee not reached (95% CI, NE–NE) **Estimated PFS at 24 months by independent review committee:** 88.9% (95% CI, 81.3–93.6) **Median PFS per investigator**: not reached (95% CI, NE–NE) **24-month PFS by investigators**: 87.0% **Estimated 24-month OS**: 93.6% (95% CI, 87.1–96.9) **ORR by independent review committee**: 90.0% (95% CI, 82.8–94.9) **ORR by investigator**: 96.4% (95% CI, 91.0–99.0) **Median duration of response by independent review committee or investigator**: NR **Complete response as assessed by independent review committee**: 6% **Patients who progressed due to Richter transformation according to investigator assessment**: 5%	**Occurrence of other cancers:** n=31/240 (13%) vs. n=20/227 (9%) **AEs leading to treatment discontinuation**: n=20/240 (8%) vs. 31/227 (14%) **Death from any cause was reported**: 16/240 (7%) vs. 14/227 (6%) **Death from AEs**: n=11 vs. n=12[4] **Group C:** **AEs:** n=109/111 (98%) **Serious AEs**: n= 45/111 (41%) **Neutropenia grade ≥3**: n=17/111 (15%) **Major bleeding events**: n=8/111 (7%) **Occurrence of other cancers**: n=24/111 (22%) **AEs leading to treatment discontinuation**: n=6/111 (5%) **Deaths:** n=8/111 (7%)[5]

Patient-reported outcomes (PROs) [10]

- PROs were secondary endpoints and assessed using the EORTC QLQ-C30 and EQ-5D-5L VAS. Patients completed these questionnaires at baseline, every 12 weeks for 96 weeks, and then every 24 weeks until disease progression, death, or withdrawal from study.
- The PRO endpoints included global health status (GHS), physical and role functions, and symptoms of fatigue, pain, diarrhoea, and nausea/vomiting, measured by QLQ-C30, with critical clinical cycles of weeks 12 and 24. Descriptive analyses were performed on all questionnaire responses, and a mixed model for repeated measures was performed on the PRO endpoints at Weeks 12 and 24.
- Baseline demographics and disease characteristics between the zanubrutinib (n=241) and BR (bendamustine +rituximab, n=238) arms were similar.
- Across all patients, adjusted completion rates for PROs were high (~80%) at weeks 12 and 24.
- Compared with patients who received BR, patients treated with zanubrutinib experienced greater improvements in HRQoL at weeks 12 and 24 as reported on the QLQ-C30.
- By week 24, significant improvements were observed with zanubrutinib vs. BR in GHS, physical functioning, role functioning as well as greater reductions in diarrhoea, fatigue, and nausea/vomiting.
- Per EQ-5D-5L VAS, comparable improvements from baseline between zanubrutinib and BR in the health status were observed at weeks 12 (4.3 vs. 3.5) and 24 (4.5 vs. 4.9), respectively.
- Zanubrutinib was associated with significant improvements in HRQoL in pts with treatment-naïve CLL/SLL without del(17p), as indicated by the PRO endpoints of the GHS, physical and role functions, and greater reductions in symptoms of fatigue, diarrhoea and nausea/vomiting compared with BR.

ESMO-MCBS version 1.1 [11]

Though not finally validated but feasibility tested in [12], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies.

[4] The most common AE leading to death in group A was COVID-19 (2%), whereas in group B these were diarrhoea and aspiration pneumonia (1%). No sudden deaths were reported.
[5] 8 of 111 patients died on study, including 4 due to disease progression and 3 due to adverse events; no patient in this group died due to COVID-19.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS was not applicable because the primary endpoint PFS was not reached.											

Risk of bias (RCT) [13]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	No, open-label	unclear[6]	yes[7]	unclear

Study characteristics: ALPINE trial [14-16]								
Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ALPINE, BGB-3111-305 NCT03734016	415 1:1	zanubrutinib (160 mg twice daily)	ibrutinib (420 mg once daily)	investigator-assessed ORR	**ongoing**[8], global, open-label, randomised, phase 3 study	-	BeiGene	[14] (abstract) [19]

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>First pre-planned interim analysis data (conducted ~12 months after 415 patients enrolled between November 2018 and December 2019); only abstract available:</u> **ORR** (with a median follow-up of 15 months): 78.3% vs. 62.5%; 2-sided p=0.0006, pre-specified α=0.0099 **ORR in patients with del(11)q:** 83.6% vs. 69.1% **ORR in patients with and del(17)p**: 83.3% vs. 53.8% **Overall 12-month PFS**: 94.9% vs 84.0% **OS:** 97.0% vs 92.7% **<u>UPDATE: ALPINE trial final analysis (median follow-up 29.6 months) [17-19]:</u>** **Overall Response:** ORR (investigator-assessed): 83.5% vs. 74.2% ORR (by IRC): 86.2% vs. 75.7% PR with lymphocytosis or better (investigator-assessed): 89.9% vs. 82.5% DOR (as assessed by both the investigators and the IRC): NR vs. 33.9 months Event-free response at 24 months (investigator assessed): 79.5% vs. 71.3% Event-free response at 24 months (by the IRC): 77.4% vs. 67.8% **Progression-free survival:** Disease progression or death: 26.6% vs. 36.3%; HR 0.65; 95% CI, 0.49-0.86; p= 0.002 PFS at 18 months (investigator-assessed): 83.3% (95% CI, 78.7-87.0) vs. 75.0% (95% CI, 69.8 to 79.4) in the ibrutinib PFS at 24 months: 78.4% (95% CI, 73.3-82.7) vs. 65.9% (95% CI, 60.1-71.1) Median PFS: NR vs. 34.2 months (95% CI, 33.-NE) PFS in a prespecified subgroup of high-risk patients with 17p deletion, TP53 mutation, or both (investigator-assessed): 32.0% vs. 48.0%; HR 0.53; 95% CI, 0.31-0.88	**Patients with atrial fibrillation/flutter:** 2.5% vs 10.1%, 2-sided p=0.0014, pre-specified α=0.0099 **Patients with major bleeding:** 2.9% vs. 3.9% **AEs leading to discontinuation:** 7.8% vs. 13.0% **AEs leading to death:** 3.9% vs. 5.8% **Patients with neutropenia rate:** 28.4% vs. 21.7% **Patients with grade ≥3 infections:** 12.7% vs. 17.9% **<u>UPDATE: ALPINE trial final analysis (median follow-up 29.6 months) [17-19]</u>** ≥1 AE: n= 318/324 (98.1%) vs. n=321/324 (99.1%) Grade ≥3 AEs: n=218/324 (67.3%) vs. n=228/324 (70.4%) All serious AEs: n=136/324 (42.0%) vs. n=162/324 (50.0%) Events leading to dose reduction: n=40/324 (12.3%) vs. n=55/324 (17.0%) Events leading to dose interruption: n=162/324 (50.0%) vs. n=184/324 (56.8%) Events leading to treatment discontinuation: n=50/324 (15.4%) vs. n=72/324 (22.2%) Events leading to death: n=33/324 (10.2%) vs. n=36/324 (11.1%)

[6] The SEQUOIA trial is ongoing.
[7] BeiGene sponsored and funded the study and was involved in study design and data analyses with the study steering committee. Trial investigators, including all non-sponsor authors, collected data during the trial. The sponsor managed the study database, supplied the study drug, and provided editorial assistance.
[8] The ALPINE trial is currently ongoing; estimated study completion date is 08/2023.

PFS in a prespecified subgroup of high-risk patients with 17p deletion, TP53 mutation, or both (by IRC): 30.7% vs. 45.3%; HR 0.52; 95% CI, 0.30-0.88) Patients in this high-risk population who were alive without disease progression at 24 months: 72.6% (95% CI, 60.3-81.7) vs. 54.6% (95% CI, 40.7-66.4) Patients free from treatment failure at 24 months: 79.9% (95% CI, 75.1-83.9) vs. 65.0% (95% CI, 59.5-70.0) **Overall Survival** Deaths: 14.7% vs. 18.5%; HR 0.76 (95% CI, 0.51-1.11) Median OS: NR vs. NR	

Health-related QoL (HRQoL) outcomes [20]

- HRQoL was examined by PROs measures assessed by EORTC QLQ-C30 and EQ-5D-5L at baseline, Cycle 1, and then every 3rd cycle until end of treatment.
- Key PRO endpoints included GHS, physical and role functions, and fatigue, pain, diarrhoea, and nausea/vomiting. Descriptive analysis on all the scales was conducted as was a mixed model repeated-measure analysis of the longitudinal QLQ-C30 data.
- Data presented are from key cycles (7 and 13), corresponding to 6 and 12 months of treatment, respectively.
- In the ITT population (N=652; zanubrutinib, n=327; ibrutinib, n=325), adjusted completion rates were high (>85%) in both arms at Cycles 7 and 13.
- On the QLQ-C30, estimated mean treatment differences and 95% CI in key PRO endpoints demonstrated treatment differences, in favour of zanubrutinib, in GHS, physical functioning, and fatigue in Cycle 7, and diarrhoea in Cycle 13.
- Mean change from baseline (SD) in EQ-5D-5L VAS showed consistently more improvement with zanubrutinib compared with ibrutinib at both Cycle 7: 8.4 (18.2) vs. 4.0 (16.6) and Cycle 13: 6.8 (18.8) vs. 5.2 (17.5).

  In the ALPINE trial, patients with relapsed/refractory CLL/SLL who received zanubrutinib monotherapy reported improvements in key HRQoL endpoints compared with patients who received ibrutinib monotherapy.

ESMO-MCBS version 1.1 [11]

Disclaimer: Though not finally validated, but feasibility tested in [12], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, the original ESMO assessments were also carried out for haematological indications in new fact sheets and updates

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Not applicable due to the primary endpoint (ORR).											

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	no, open-label	yes	yes[9]	unclear

First published: 11/2022
Last updated: 02/2023

Abbreviations: AE=adverse event, AJ=adjustment, BSA=body surface area, BR=bendamustine+rituximab, BTK=Bruton tyrosine kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukaemia, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GHS=global health status, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, Int.=intention, ITT=intention-to-treat, IV=intravenous, MCL=mantle cell lymphoma, MZL=marginal zone lymphoma, MG=median gain, n=number of patients, NE=not estimable, NICE=National Institute for Health and Care Excellence, NR=not reached, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PROs=patient-reported outcomes, QoL=quality of life, SAE=serious adverse event, SLL=small lymphocytic lymphoma, ST=standard treatment, VAS=visual analogue scale

[9] The trial protocol was developed by the sponsor in collaboration with the trial investigators. The sponsor was also involved in the collection, analysis, and interpretation of the data. Statistical analyses were performed by statisticians at BeiGene. The initial draft of the manuscript was written by the first and 22nd authors with assistance from a medical writer who was an employee of the sponsor. All the authors provided critical revision and approved the version of the manuscript to be submitted for publication.

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