Acalabrutinib (Calquence®) for the treatment of chronic lymphocytic leukaemia (CLL)

General information [1]

Drug description	Indication
Acalabrutinib is a protein kinase inhibitor which acts by inhibiting the Bruton tyrosine kinase, thus preventing signalling for B-cell survival and proliferation and resulting in blocking cellular adhesion, trafficking, and chemotaxis.	Acalabrutinib is indicated as ❖ monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL ❖ monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy.

Current treatment [2]

The following first-line treatment recommendations have been made by NICE for patients with CLL:

- ❖ Venetoclax is recommended for use as an option for treating CLL, that is in adults with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable
- ❖ Ibrutinib alone is recommended as an option for treating CLL in adults who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable
- ❖ Idelalisib as a first-line therapy in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies
- ❖ Idelalisib, in combination with rituximab, is recommended for untreated CLL in adults with a 17p deletion or TP53 mutation
- ❖ Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable
- ❖ Bendamustine is recommended as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
- ❖ Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.

Regulatory status

EMA [1]	FDA [3, 4]
Approval status for this indication: On 23 July 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Calquence®, intended for the treatment of CLL. Date of issue of marketing authorisation valid throughout the European Union: 05/11/2020 The full indication is: Calquence® as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. Calquence® as monotherapy is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. **Other indications**: none ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 21 November 2019, the FDA approved acalabrutinib for adults with CLL or SLL. **Other indications**: Acalabrutinib is indicated for the treatment of adult patients with: ❖ Mantle cell lymphoma (MCL) who have received at least one prior therapy (accelerated approval)

Costs

60 Calquence hard capsules 100 mg = € 7,126.00 (ex-factory price) [5]
ELEVATE-TN- and ASCEND trial patients received 100 mg acalabrutinib twice daily [6]; costs for **30 days of acalabrutinib treatment → € 7,126.00.**

Study characteristics : ELEVATE-TN trial [7, 8]

Trial name	*n*	Intervention (I1)	Intervention (I2)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ELEVATE-TN NCT02475681	535 (1:1:1 ratio)	acalabrutinib (100 mg twice	acalabrutinib (100 mg	obinutuzumab + chlorambucil	PFS between the two combination-therapy groups	phase 3, randomised, multicentre, open-label study	-	Acerta Pharma, a member of the AstraZeneca Group, and R35 CA198183 (to JCB)	Link

		a day) + obinutuzumab	twice daily) monotherapy						

Efficacy (I vs. C)	Safety (I vs. C)
Combination: median PFS after a median follow-up of 28.3 months: statistically significantly longer with acalabrutinib-obinutuzumab (not reached, 95% CI not evaluable–not evaluable) than with obinutuzumab-chlorambucil (22.6 months, 20.2–27.6), with a 90% reduction in relative risk of progression or death with acalabrutinib-obinutuzumab (HR 0.10, 0.06–0.17; p<0.0001). **Monotherapy: median PFS** was significantly longer with acalabrutinib monotherapy (not reached, range 34.2–not evaluable) versus obinutuzumab-chlorambucil (22.6, 95% CI 20.2–27.6) HR 0.20, 95% CI 0.13–0.30; p<0.0001). **Estimated PFS at 24 months**: was 93% (combination, 95% CI 87–96%) vs. 87% (monotherapy, 81–92%) vs. 47% (control, 39–55%). **HR for PFS** between acalabrutinib-obinutuzumab and acalabrutinib monotherapy was 0.49 (95% CI 0.26–0.95, post-hoc analysis). **Median time to event** (among the patients with disease progression or death): 12.7 months (IQR 8.3–20.2) vs. 13.9 months (5.7–23.4) vs. 16.4 months (11.8–21.0) **Best overall response rate:** statistically significantly better with acalabrutinib-obinutuzumab (94%, 95% CI 89–97%) vs. obinutuzumab-chlorambucil (79%, 72–84%; p<0.0001). **Overall response** was 86% for acalabrutinib monotherapy (95% CI 80–90%, p=0.08) vs. obinutuzumab-chlorambucil. **Complete response** (ICR-assessed; including complete response with incomplete bone marrow recovery): 24 (13%) of 179 patients with acalabrutinib-obinutuzumab vs. 8 (5%) of 177 patients with obinutuzumab-chlorambucil; one (1%) of 179 patients had complete response with acalabrutinib monotherapy. **Median OS:** not reached in any group (acalabrutinib-obinutuzumab vs. obinutuzumab-chlorambucil HR 0.47, 95% CI 0.21–1.06; p=0.06; acalabrutinib monotherapy vs. obinutuzumab-chlorambucil 0.60; 0.28–1.27, p=0.16) **Estimated OS at 24 months**: 95% (95% CI 91–97%) vs. 95% (90–97%) vs. 92% (86–95%) **Median time to next treatment:** not reached in any group; the risk of needing a subsequent therapy was reduced with acalabrutinib-obinutuzumab (HR 0.14, 95% CI 0.08–0.26; p<0.0001) and acalabrutinib monotherapy (0.24, 0.15–0.40; p<0.0001) compared with obinutuzumab-chlorambucil.	**Grade ≥3 AEs**: n=125/178 (70.2%) vs. n=89/179 (49.7%) vs. n=118/169 (69.8%) **Any grade SAEs:** n=69/178 (38.3%) vs. n=57/179 (31.8%) vs. n=37/169 (21.9%) **Deaths from any cause[1]:** n=8/178 (5%) vs. n=12/179 (7%) vs. n=15/169 (9%) Deaths due to AEs: n=4/178 (2%) vs. n=6/179 (3%) vs. n=11/169 (7%) **AEs that led to drug discontinuation** (any grade): n=20/178 (11.2%) vs. n=16/179 (8.9%) vs. n=25/169 (14.1%)

Risk of bias[2] (study level)

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	no, open-label	unclear[3]	yes[4]	unclear

Study characteristics – ASCEND trial [5] [6, 9, 10]

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ASCEND NCT02970318	310	acalabrutinib monotherapy (100 mg twice daily)	investigator's choice: idelalisib plus rituximab (I-R) or bendamustine plus rituximab (B-R)	PFS (by IRC) in the ITT-population	randomized, global, multicenter, open-label, phase 3 study	-	Acerta Pharma	Link

Efficacy (I vs. C)	Safety (I vs. I-R vs. B-R)
Median PFS (after a median follow-up of 16.1 months): significantly longer with acalabrutinib monotherapy (PFS not reached) compared with investigator's choice (16.5 months; 95% CI, 14.0 to 17.1 months); HR 0.31 (95% CI, 0.20-0.49); p < .0001). **Estimated 12-month PFS** was 88% (95% CI, 81%-92%) for acalabrutinib and 68% (95% CI, 59% to 75%) for investigator's choice **Estimated 15-months PFS** was 82.6 % (75.0-88.1) vs. 54.9% (45.4-63.5) **Overall response rate**: 81% vs. 76%, p=0.22	**Grade 3 or 4 AEs**: n=70/154 (45%) vs. n=101/118 (86%) vs. n=15/35 (43%) **SAEs:** n=44/154 (29%) vs. n=66/118 (56%) vs. n=9/35 (26%) **Death:** n=15/154 (10%) vs. n=13/118 (11%) vs. n=5/35 (14%) **Grade 5 AEs**: n=6/154 (4%) vs. n=5/118 (4%) vs. n=2/35 (6%)

[1] Death from any cause; including 4 deaths from CLL disease progression (2 vs. 1 vs. 1), 2 deaths due to Richter's transformation and 21 deaths due to AEs
[2] ELEVATE-TN trial
[3] ELEVATE-TN trial is ongoing until 07/2021
[4] Acerta Pharma sponsored the study and was involved in the study design and data analyses with the lead investigators
[5] Only abstracts available

Median duration of response: NR vs. 13.6 months, HR 0.33, p<0.0001 **12-month duration of response rate**: 85% vs. 60% **Long term follow-up efficacy results per investigator assessment assessments (with long term data, the median follow-up was 22.1 months for acalabrutinib monotherapy and 21.9 months for investigator´s choice):** **Median PFS:** NR vs. 16.8 months, HR 0.27 (95% CI, 0.18-0.40) **Estimated 21-months PFS:** 79.1 months vs. 45.3 months **OS, death events:** 21% vs. 26% **ORR:** 80% vs. 83.9% **Median duration of response:** NR vs. 18 months	**Discontinuation[6]:** n=17/154 (11%) vs. n= 58/118 (49%) vs. n=6/36 (17%)
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Abbreviations: AE=adverse event, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukaemia, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, ICR=independent review committee, ITT=intention-to-treat, n=number, MCL=mantle cell lymphoma, MRD=minimal residual disease, n=number of patients, NR=not reached, SAE=serious adverse event, SLL= small lymphocytic lymphoma, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, SAE=serious adverse event, SLL=small lymphocytic lymphoma

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[6] Discontinuation due to AE(s)

10. Ghia P, Pluta A, Wach M, Lysak D, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia [Available from: https://ascopubs.org/doi/abs/10.1200/JCO.19.03355.