swissmedic

Date: 12 November 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Calquence

International non-proprietary name: acalabrutinib as acalabrutinib maleate monohydrate

Pharmaceutical form:	film-coated tablets
Dosage strength(s):	100 mg
Route(s) of administration:	oral
Marketing authorisation holder:	AstraZeneca AG
Marketing authorisation no.:	68817
Decision and decision date:	extension of therapeutic indication approved on 7 October 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

AE	Adverse event
AV	Acalabrutinib and venetoclax
AVG	Acalabrutinib, venetoclax, and obinutuzumab
BCL2i	B-cell lymphoma 2 inhibitor
BICR	Blinded independent central review
BR	Bendamustine and rituximab
BTKi	Bruton tyrosine kinase inhibitor
CI	Confidence interval
CIRS-G	Cumulative illness rating scale-Geriatric
CIT	Chemoimmunotherapy
CLL	Chronic lymphocytic leukaemia
DDI	Drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FCR	Fludarabin, cyclophosphamide, and rituximab
FDA	Food and Drug Administration (USA)
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGHV	Immunoglobulin heavy-chain variable region gene
IRC	Independent review committee
IWCLL	International workshop on chronic lymphocytic leukaemia
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRD	Minimal residual disease
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPI	Proton pump inhibitor
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) (see "Properties/Effects").

The applicant withdrew part of the indication initially claimed for Calquence in combination with venetoclax and obinutuzumab.

2.2.2 Approved indication

Calquence in combination with venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of acalabrutinib is 100 mg twice daily (equivalent to a total daily dose of 200 mg).
Treatment should be continued until disease progression or unacceptable toxicity or up to 14 cycles of treatment (cycles of 28 days each).

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	8 November 2024
Formal control completed	18 November 2025
List of Questions (LoQ)	17 March 2025
Response to LoQ	15 May 2025
Preliminary decision	24 July 2025
Response to preliminary decision	9 September 2025
Final decision	7 October 2025
Decision	approval

3 Medical context

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world with an average incidence of about 4.2/100,000/year, increasing to >30/100,000/year at >80 years. More male than female patients (1.7:1) are affected. Although the median age at diagnosis is 72 years, approximately 10% of CLL patients are reported to be younger than 55 years[1]. Preferred initial therapy includes continuous covalent Bruton tyrosine kinase inhibitor (BTKi)-based regimens and a fixed-duration (finite) combined B-cell lymphoma 2 inhibitor (BCL2i) + anti-CD20 monoclonal antibody. Despite recent therapeutic progress, CLL remains incurable in most cases.

[1] Eichhorst B et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32:23-33.

4 Nonclinical aspects

The applicant did not submit any new nonclinical studies to support the requested new indication, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the new indication applied for.

5 Clinical aspects

In support of the present application, data from the pivotal, open-label, randomised, controlled phase 3 study AMPLIFY (ACE-CL-311 (D8221C00001)) were submitted.

5.1 Clinical Pharmacology

Sparse PK data was collected from patients with previously untreated CLL without del(17p) or TP53 mutation enrolled in the pivotal phase 3 study ACE-CL-311/AMPLIFY. The patients in the investigational arms received the approved 100 mg twice daily acalabrutinib dose in combination with venetoclax (AV) or venetoclax/obinutuzumab (AVG).

The previously developed PK models for acalabrutinib and its active metabolite, ACP-5862, were updated using additional data from ACE-CL-311/AMPLIFY. The dataset contained 13,290 acalabrutinib and 7,902 ACP-5862 plasma concentrations from 1,569 subjects for acalabrutinib and 1174 subjects for ACP-5862 from 12 clinical studies. The PK of acalabrutinib and ACP-5862 were well described by sequential zero-order and first-order absorption with two compartments for acalabrutinib distribution, and first order elimination and a one-compartment model for its metabolite ACP-5862. In line with previous analyses, the covariate proton pump inhibitor (PPI) was included in the final population PK model. No other statistically significant covariates were identified.

Overall, the exposures were comparable across the investigational arms in ACE-CL-311/AMPLIFY and the monotherapy studies.

The combination with venetoclax or venetoclax/obinutuzumab was not identified as a statistically significant covariate in the population PK analysis. Furthermore, venetoclax serum concentrations were similar across the two treatment arms – AV and AVG – in ACE-CL-311/AMPLIFY as well as compared to historical venetoclax data following monotherapy. Overall, minimal drug-drug interaction (DDI) potential is expected.

The exposure-response relationships were investigated using data from 571 patients in ACE-CL-311/AMPLIFY. No correlation between acalabrutinib/ACP-5862 exposures and the efficacy endpoint of progression-free survival (PFS) was observed based on a Kaplan-Meier analysis and a Cox proportional hazard model. Graphical assessment indicated similar exposures across all response categories.
There was no relationship between acalabrutinib/ACP-5862 exposures and the safety endpoints of any treatment-emergent Grade ≥3 adverse events (AE) or Grade ≥3 AEs of clinical interest, AE leading to dose reductions, drug discontinuation, or dose interruption. However, it seems that toxicity is generally higher in the AVG arm.
Overall, the outcome of the exposure-response analysis is consistent with previous analyses. However, the significance of the exposure-response analysis is limited, given that only the approved 100 mg twice daily acalabrutinib dose was administered.

5.2 Dose finding and dose recommendation

There was no dedicated dose finding for the proposed AV combination treatment. Instead, approved dosages used in monotherapy and/or with different combination partners have been selected, including dosages for indications other than previously untreated CLL. No evidence was provided that lower dosages were explored, which – by taking advantage of additive or even synergistic effects from the respective drug combination – could have resulted in an improved benefit-risk balance. Exposure-efficacy analyses showed no correlation between acalabrutinib exposure and efficacy endpoints, consistent with near complete target engagement.

5.3 Efficacy

AMPLIFY included previously untreated patients aged 18 years or older with CLL without 17p deletion or TP53 mutation.

Patients with a single CIRS-G score of 4 or a total CIRS-G score >6, uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenic purpura, confirmed progressive multifocal leukoencephalopathy in their medical history, or receipt of a live-virus vaccine within 28 days prior to the first dose of the investigational product were excluded from participation. Patients were allowed to receive concomitant antithrombotic agents, except for warfarin or equivalent vitamin K antagonists.

Patients were randomised at a ratio of 1:1:1 to one of the following treatment arms (each treatment cycle lasted 28 days):

1. **AV**: Acalabrutinib 100 mg was administered twice daily starting on day 1 of cycle 1 for a total of 14 cycles or until disease progression or unacceptable toxicity occurred. On day 1 of cycle 3, patients began a 5-week venetoclax dose escalation schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg, and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles.
2. The same treatment as in the AV arm was administered with in addition obinutuzumab from Cycle 2 through Cycle 7.
3. **CIT**:
    - **FCR**: Fludarabine (25 mg/m²) and cyclophosphamide (250 mg/m²) were administered on days 1–3 of up to a maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m² on day 1 of cycle 1 and at a dose of 500 mg/m² on day 1 of cycle 2 up to a maximum of 6 cycles.
    - **BR**: Bendamustine 90 mg/m² was administered on days 1 and 2 of up to a maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m² on day 1 of cycle 1 and at a dose of 500 mg/m² on day 1 of cycle 2 up to a maximum of 6 cycles.

Patients were stratified by age (>65 years or ≤65 years), IGHV mutation status (mutated versus unmutated), Rai stage (high risk [≥3] versus not high risk), and geographic region (North America versus Western Europe versus other). Table 7 summarises the baseline demographic and disease characteristics of the treatment arms.

Table 7. Baseline characteristics of patients (AMPLIFY) with previously untreated CLL

Characteristic	AV (N=291)	CIT (N=290)
Age, years; median (range)	61 (31–84)	61 (26–86)
Male, %	61.2	63.1
Caucasian, %	91.1	86.9
ECOG performance status 0–1, %	90.0	90.3
Median time from diagnosis to randomisation (months)	28.5	29.6
Bulky disease with lymph nodes ≥5 cm, %	38.8	42.8
Cytogenetic/FISH category, %		
11q deletion	17.5	15.9

Characteristic	AV (N=291)	CIT (N=290)
Complex karyotype (≥3 abnormalities)	15.5	14.5
Unmutated IGHV, %	57.4	59.3
Rai stage, %		
0	1.0	1.4
I	16.2	21.4
II	35.7	33.4
III	23.7	20.3
IV	23.4	23.4

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC) for the AV arm versus CIT (FCR/BR) based on the 2018 IWCLL criteria. Additional efficacy endpoints included minimal residual disease (MRD) in peripheral blood, measured by flow cytometry (10^{-4}), and overall survival (OS). The MRD comparison was based on cycle 9 (AV) or 12 weeks after the start of cycle 6 (FCR/BR).

After a median follow-up of 41.3 months, the IRC-assessed PFS in patients treated with AV showed a statistically significant reduction in the probability of disease progression or death compared to CIT, with a hazard ratio (HR]) of 0.65 (95% CI 0.49; 0.87). The benefit of acalabrutinib in combination with venetoclax in terms of PFS risk reduction was consistent in the subgroup of CLL patients with unmutated IGHV.

MRD negativity at the above-mentioned time points was achieved in 78 (26.8%) of the AV-treated patients and 148 (51.0%) of the CIT-treated patients (relative risk favouring the FCR/BR arm: 0.5 (95% CI 0.4; 0.7).

After a median follow-up of 46.4 months, the OS HR was 0.42 (95% CI 0.25; 0.70) for the AV arm compared to the CIT arm, with a total of 67 deaths – 23 (7.9%) in the AV arm and 44 (15.2%) in the CIT arm. However, as the statistical testing procedure could not proceed due to the MRD result, statistical significance for the OS outcome could not be established.

5.4 Safety

All 291 patients randomised into the AV arm of the pivotal AMPLIFY study, and 259 of 290 patients in the CIT arm received at least one dose of any study treatment and were included in the safety population. As of data cut-off on 30 April 2024, the median duration of study treatment was 12.9 months for acalabrutinib-based therapy, and 5.6 months for CIT.

More than 90% of patients in both treatment arms reported at least 1 treatment-emergent AE (TEAE).

Gastrointestinal TEAEs had the highest incidence across the treatment arms. While their overall incidence was similar across arms (approximately 55%), diarrhoea occurred more frequently in the AV arm than in the CIT arm, 32.6% vs 11%, whereas nausea was more common on CIT (35.9%) vs. AV (14.8%). Gastrointestinal side effects were already labelled in the Calquence Information for healthcare professionals.

Infections were the next most common TEAEs occurring in the majority of patients in the AV arm (50.9%) vs 31.7% in the CIT arm. In particular, more patients suffered from COVID-19 (18.9% vs 2.3%) and COVID-19 pneumonia (7.2% vs 2.7%). Infections were already labelled for Calquence,

including a pertinent warning. However, COVID-19 infections, especially in CLL patients, needed more emphasis, and were included in the updated Information for healthcare professionals.

Between 40 to 50% of patients across treatment arms reported haematological TEAEs, mostly neutropenia in 30 to 40%, with patients in the AV arm reporting incidences at the lower end of the range compared to the CIT arm. Cytopenia was already labelled for Calquence, including a pertinent warning. A notably higher incidence of febrile neutropenia was observed for CIT (9.3%) compared to AV (1.7%).

More patients in the AV arm reported musculoskeletal and connective tissue disorders – 37.1% vs 18.1% in the CIT arm – mainly due to higher incidences of musculoskeletal pain such as arthralgia, back pain, myalgia and pain in the extremities. Musculoskeletal pain was already labelled for Calquence.

Substantially more patients in the AV arm reported headache, which is a known side effect of acalabrutinib: 35.1% vs 7.7% in the CIT arm.

Haemorrhages were more frequent in the AV arm (32.3% vs 4.2% in the CIT arm), while the difference was less pronounced for Grade ≥ 3 haemorrhages (1.0% vs 0.4%) and major haemorrhages (1.0% vs 0.8%). Contusions were the most frequently reported haemorrhage event for AV treatment, and more patients reported them in the acalabrutinib arm (13.7% vs. 1.75% in the CIT arm). Bleeding is a known side effects of BTKi therapy, and the Calquence Information for healthcare professionals already included a pertinent warning.

Patients in the AV arm experienced more cardiac disorders than those in the CIT arm (9.3% vs.3.5%), which was mainly due to a greater incidence of palpitations and tachycardia. While the latter was mostly of supraventricular origin, ventricular tachycardia was reported in one patient in the AV arm. The number of patients experiencing atrial fibrillation was comparable between the AV and control CIT arm (two patients each, <1%). Atrial fibrillation was already labelled for Calquence.

Infusion-related reactions were reported in the CIT (32.8%) but not in the AV arm.

Grade ≥ 3 AEs occurred in 53.6% and 60.6% of patients in the AV and the CIT arm, respectively. The Grade ≥ 3 TEAE with the highest incidence (reported in ≥10% of patients in any arm) was neutropenia in both arms (26.8% and 32.4%, respectively).

The incidence of serious AEs (SAEs) was 24.7% and 27.4% in the AV and the CIT arm, respectively. The SAEs with the highest incidences (reported in ≥ 5% of patients) were COVID-19 pneumonia (5.8%) in the AV arm and febrile neutropenia (8.1%) in the CIT arm.

The incidence of on-treatment (treatment-emergent) fatal (grade 5) AEs was comparable between the AV arm (10 patients, 3.4%) and the CIT arm (9 patients, 3.5%). The most common single cause of death was COVID-19-related TEAEs, again with similar incidences reported across both arms (8 patients (2.7%) vs 7 patients (2.7%)). However, these results have to be interpreted in the light of the substantially lower proportion of vaccinated patients in the CIT arm compared to the AV arm.

The incidence of AEs leading to discontinuation of any study treatment was 7.9% in the AV arm and 10.8% in the CIT arm. The most common TEAEs leading to discontinuation were COVID-19 pneumonia in the AV arm, and thrombocytopenia and (febrile) neutropenia in the CIT arm.

The incidence of AEs leading to dose reduction of any study treatment was 14.1% in the AV arm and 11.2% in the CIT arm. In both treatment arms neutropenia / neutrophil count decreased was the most common AE that led to dose reduction.

The incidence of AEs leading to dose withholding of any study treatment was 49.8% in the AV arm, and 31.3% the CIT arm. The most frequently reported TEAEs (≥ 10% of patients in either arm) leading to drug withholding of any treatment in each arm were neutropenia (23.0% [AV arm] vs 13.5% [CIT arm]) and COVID-19 (10.3% [AV arm] vs 0.4% [CIT arm]).

The analysis of events of clinical interest showed that patients in the AV arm experienced more second primary malignancies than those in the CIT arm (5.2% vs. 0.8%). This imbalance remained

after non-melanoma skin malignancies were excluded (2.7% vs. 0.4%). Second primary malignancies were already labelled for Calquence, including a pertinent warning.

5.5 Final clinical benefit risk assessment

The pivotal AMPLIFY study met its primary endpoint of blinded independent central review (BICR)-assessed PFS for the AV combination compared to CIT with FCR/BR. Although OS results were only nominal due to the failure to meet statistical significance for the MRD negativity rate, they favoured the AV arm over the CIT arm.

The reported safety profile of AV was consistent with earlier safety data, and included, among others, gastrointestinal side effects, infections, cytopenia, musculoskeletal pain, headache, bleeding, cardiac disorders, and second primary malignancies.

Overall, the benefit-risk balance of the proposed AV combination was assessed as positive. For the AVG combination the benefit-risk was assessed as negative and the applicant withdrew this part of the indication.

The submission of the final clinical study report of the AMPLIFY study by the end of 2027, including final OS results and updated Information for healthcare professionals, was mandated as a post-authorisation requirement.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Calquence was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Calquence has temporarily approved indications, see section "Indications/uses".

CALQUENCE, film-coated tablets

Composition

Active substances

Acalabrutinib (as acalabrutinib maleate monohydrate)

Excipients

Tablet Core:
Mannitol (E421)
Microcrystalline cellulose
Low-substituted hydroxypropyl cellulose
Sodium stearyl fumarate
Tablet Coating:
Hypromellose
Copovidone
Titanium dioxide (E171)
Macrogol 3350
Medium-chain Triglycerides
Yellow iron oxide (E172)
Red iron oxide (E172)
1 film-coated tablet contains 0.59 mg sodium.

Pharmaceutical form and active substance quantity per unit

Each film-coated tablet contains acalabrutinib maleate equivalent to 100 mg of acalabrutinib.
The Calquence 100 mg tablet is an orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with «ACA 100» on one side and plain on the reverse.

Indications/Uses

Temporarily authorised indication

Mantle Cell Lymphoma (MCL)

CALQUENCE in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated MCL who are not suitable for autologous stem cell transplantation (see "Warnings and Precautions" and "Properties/Effects").
Due to incomplete documentation at the time of the assessment of the application, this indication was authorized for a limited period of time (Art. 9a Therapeutic Products Act). The temporary authorization is mandatory subject to the timely fulfillment of conditions. Once this has been achieved, the temporary marketing authorization can be changed to a marketing authorization without any specific requirements.
Indications with non-limited authorisation

Mantle cell lymphoma (MCL)
CALQUENCE as monotherapy is indicated for the treatment of adult patients with MCL who have not achieved any partial response with prior therapy or who have experienced progression after prior therapy (see “Properties/Effects”).
Chronic lymphocytic leukaemia (CLL)
CALQUENCE monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL who are 65 years and older or have comorbidities (see “Properties/Effects”).
CALQUENCE monotherapy is indicated for the treatment of adult patients with CLL who have received at least one prior therapy (see “Properties/Effects”).
CALQUENCE in combination with venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see “Properties/Effects”).

Dosage/Administration

Treatment with CALQUENCE should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Usual dosage

MCL
The recommended dosage of CALQUENCE as monotherapy is 100 mg (1 tablet) twice daily.
The recommended dose of CALQUENCE in combination with other medicinal products is 100 mg (1 tablet) twice daily. For the combination regimens, refer to the prescribing information of each of the medicinal product for dosing information. For details of the combination regimens, see section “Properties/effects”.
Treatment with CALQUENCE should continue until disease progression or unacceptable toxicity.

CLL

The recommended dose of CALQUENCE for the treatment of CLL is 100 mg (1 tablet) twice daily, either as monotherapy or in combination. Refer to the prescribing information of each of the combination medicinal products for recommended dosing information (for details of the combination regimens, see section “Properties/Effects”).

CALQUENCE doses should be separated by approximately 12 hours.

Treatment with CALQUENCE monotherapy or in combination with obinutuzumab should continue until disease progression or unacceptable toxicity.

Treatment with CALQUENCE in combination with venetoclax, should continue until disease progression, unacceptable toxicity or completion of 14 cycles of treatment (each cycle is 28 days).

Mode of administration

CALQUENCE should be swallowed whole with water at approximately the same time each day every 12 hours. CALQUENCE can be taken with or without food. The tablet should not be chewed, crushed, dissolved, or divided.

Missed dose

If a patient misses a dose of CALQUENCE by more than 3 hours, instruct the patient to take the next dose at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

Dose adjustment following undesirable effects/interactions

Recommended dose modifications of CALQUENCE monotherapy and as combination therapy with Obinutuzumab, see Table 1. Calquence dose modifications for adverse reactions in patients receiving Calquence in combination with venetoclax are listed in Table 2.

Recommended dose modifications for Grade ≥ 3 adverse reactions in patients receiving CALQUENCE in combination with bendamustine and rituximab are provided in Table 3.

Please also consult the Information for healthcare professionals of the respective combination product regarding dose adjustments.

Table 1. Recommended Dose Adjustments for Adverse Reactions in patients receiving CALQUENCE monotherapy and Calquence in combination with obinutuzumab*

Adverse reaction	**Adverse reaction occurrence**	**Dose modification** (Starting dose = 100mg approximately every 12 hours)
Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia Or	First and second	Interrupt Calquence Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at 100 mg approximately every 12 hours

Grade 4 neutropenia lasting longer than 7 days Any other unmanageable Grade 3 or any other Grade 4 toxicities	Third	Interrupt Calquence Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at a reduced frequency of 100 mg once daily
	Fourth	Discontinue Calquence

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Table 2. Recommended dose modifications for adverse reactions in patients receiving CALQUENCE in combination with venetoclax.

Adverse reaction[a]	**Adverse reaction occurence**	**CALQUENCE dose modification**
Grade 3 or 4 neutropenia with or without fever and/or infection; Grade 4 neutropenia lasting more than 7 days	First occurrence	Interrupt CALQUENCE and/or venetoclax.[b] Once toxicity resolves to Grade ≤1 or baseline, restart CALQUENCE and/or venetoclax at same dose.
	Second occurrence	Interrupt CALQUENCE and venetoclax.[b] Once toxicity resolves to Grade ≤1 or baseline, restart CALQUENCE at same dose and venetoclax at one lower dose level.
	Subsequent occurrence	Interrupt CALQUENCE and venetoclax until toxicity resolves to Grade ≤1 or baseline.[b] Clinical judgment of the treating physician should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with CALQUENCE in combination with venetoclax. Discontinue Calquence at 4th adverse reaction occurrence.
Grade 3 or 4 thrombocytopenia and/or bleeding[c]	First occurrence	Interrupt CALQUENCE and/or venetoclax. When bleeding resolves and thrombocytopenia is Grade ≤1 or baseline without transfusion support for 5 consecutive days, restart CALQUENCE and/or venetoclax at same dose.

	Second occurrence	Interrupt CALQUENCE and venetoclax until resolution of bleeding and thrombocytopenia resolves to Grade ≤1 or baseline. Restart CALQUENCE at same dose and/or restart venetoclax at one lower dose level.
	Subsequent occurrences of severe thrombocytopenia	Interrupt CALQUENCE and venetoclax until resolution of bleeding and thrombocytopenia resolves to Grade ≤1 or baseline. Restart CALQUENCE at a reduced frequency of 100 mg once daily and/or venetoclax at one lower dose level. For recurrent severe thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, the clinical judgment of the treating physician should guide the management plan. Discontinue Calquence at 4th adverse reaction occurrence.
Grade 3 or 4 tumour lysis syndrome (TLS), first episode and subsequent episodes	First and subsequent episodes	If a subject experiences blood chemistry changes suggestive of TLS, the following day's venetoclax and CALQUENCE dose should be withheld. If resolved within 24‑48 hours of last dose, treatment can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, venetoclax should be resumed at one lower dose level. When resuming treatment after interruption due to TLS, monitor for TLS and provide prophylaxis.
Grade 2 other nonhematologic events[d]	Any occurence	Interrupt CALQUENCE and/or venetoclax if deemed clinically indicated until it resolves to Grade ≤1. Restart CALQUENCE and/or venetoclax at same dose.
Grade 3 other nonhematologic events[d]	First occurrence	Interrupt CALQUENCE and/or venetoclax until toxicity resolves to Grade ≤1. Restart CALQUENCE and/or venetoclax at same dose.

	Second occurrence	Interrupt CALQUENCE and/or venetoclax until toxicity resolves to Grade ≤1. Clinical judgment of the treating physician should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with CALQUENCE in combination with venetoclax.
Grade 4 other nonhematologic events[d]	First occurrence	Interrupt CALQUENCE and/or venetoclax until toxicity resolves to Grade ≤1. Restart CALQUENCE at a reduced frequency of 100 mg once daily and/or venetoclax at one lower dose level.
	Second occurrence	Interrupt CALQUENCE and/or venetoclax until toxicity resolves to Grade ≤1. Clinical judgment of the treating physician should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with CALQUENCE in combination with venetoclax.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[b] Growth factor may be used at physician discretion.

[c] Platelets may be used at physician discretion.

[d] Certain treatment-emergent non-hematologic AEs (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤1 according to the NCI CTCAE definitions. In such cases, if a subject is clinically stable, resumption of study drug may be possible based on clinical judgement of the treating physician.

Table 3. Recommended dose adjustments for Grade ≥ 3 adverse reactions* in patients receiving CALQUENCE in combination with bendamustine and rituximab

Adverse reaction	**Bendamustine dose modification†**	**Calquence dose modification**
Neutropenia	If Grade 3 or Grade 4 neutropenia: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level,	If Grade 4 neutropenia lasting longer than 7 days then interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced

Adverse reaction	Bendamustine dose modification†	Calquence dose modification
	bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	frequency of 100 mg once daily (2nd and 3rd adverse reaction occurrence). Discontinue Calquence at 4th adverse reaction occurrence.
Thrombocytopenia	If Grade 3 or Grade 4 thrombocytopenia: Interrupt bendamustine. Once toxicity has resolved to Grade 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	If Grade 3 thrombocytopenia with significant bleeding or Grade 4 then interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd occurrence). Discontinue Calquence at 3rd adverse reaction occurrence for thrombocytopenia with significant bleeding. Discontinue Calquence at 4th adverse reaction occurrence.
Other hematologic Grade 4‡ or unmanageable Grade 3 toxicity	Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	Interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd adverse reaction occurrence). Discontinue Calquence at 4th adverse reaction occurrence.
Grade 3 or greater non-hematologic toxicities	Interrupt bendamustine. Once toxicity has resolved to Grade 1 or baseline level, bendamustine may be resumed at 70 mg/m^2.	Interrupt Calquence. Once toxicity has resolved to Grade 2 or baseline, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd adverse reaction

Adverse reaction	Bendamustine dose modification†	Calquence dose modification
	Discontinue bendamustine if additional dose reduction is required.	occurrence). Discontinue Calquence at 3rd adverse reaction occurrence.

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

†For any toxicities not listed in this table refer to the bendamustine local prescribing information.

‡ Grade 4 lymphopenia is an expected outcome for treatment with bendamustine and rituximab. Dose modification due to lymphopenia is expected only if considered clinically important by investigators e.g. associated recurrent infections.

Refer to the prescribing information of each of the medicinal products used in combination with Calquence for additional information for management of toxicities.
Recommendations regarding use of Calquence with CYP3A inhibitors or inducers are provided in Table 4.

Table 4. Use with CYP3A Inhibitors or Inducers

	Co-administered Medicinal Product	**Recommended CALQUENCE Use**
CYP3A Inhibitors	Strong CYP3A Inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitors	No dose adjustment. Patients should be closely monitored for adverse reactions when taking moderate CYP3A4 inhibitors concomitantly.
CYP3A Inducers	Strong CYP3A Inducers	Avoid concomitant use; consider alternative agents with lower CYP3A induction.

Special dosage instructions

Patients with impaired renal function

No dose adjustment is recommended in patients with mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73m^2 as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics and safety of CALQUENCE in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or end-stage renal disease have not been studied (see section “Pharmacokinetics”).

Patients with impaired hepatic function

No dose adjustment is recommended in patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B, or total bilirubin between 1.5-3 times the upper limit of normal [ULN] and any AST). It is not recommended to administer CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN and any AST) (see section “Pharmacokinetics”).

Elderly patients (≥ 65 years)

No dose adjustment is necessary based on age (see section «Pharmacokinetics»).

Children and adolescents

The safety and efficacy of CALQUENCE in children and adolescents aged less than 18 years have not been established.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Second Primary Malignancies

A second primary tumour has been described in 17.6% of patients with haematologic malignancies receiving CALQUENCE as monotherapy (n=1478) and in 12.1 of patients treated with CALQUENCE in combination with other medicinal products (n=1095). These were skin neoplasms and other neoplasms. The most frequent second primary malignancy was non-melanoma skin cancer, which occurred in 9.9% (all grades) of patients treated with CALQUENCE monotherapy and in 7.2 of patients treated with CALQUENCE in combination with other medicinal products. The most frequent second primary malignancy, excluding non-melanoma skin, included prostate cancer (1.3% and 0.6%, respectively), squamous cell carcinoma (1.2% and 1.3%, respectively), and malignant melanoma (0.9% and 0.5%, respectively).
Patients must be monitored for the occurrence of secondary malignancies and should avoid sun exposure.

Infections

Infections have occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy (74.3%, n=1478) and treated with combination therapy of CALQUENCE with other medicinal products (66.1, n=1095), most often due to upper respiratory tract infections (25.8% and 16.5%, respectively), COVID-19 infections (8.5% and 26.3%, respectively) inclusive COVID-19 pneumonia (2.0% and 10.4%, respectively), pneumonia (15.8% and 9.7%%, respectively), and sinusitis (11.4% and 6.7%, respectively). Serious infections (bacterial, viral or fungal infections), including fatal events have occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy (25.3%) and treated with combination therapy of CALQUENCE with other

medicinal products (27.0%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia. Infections due to hepatitis B virus (HBV) and herpes zoster virus (HSV) reactivation, aspergillosis and progressive multifocal leukoencephalopathy (PML) have occurred (see section “Undesirable effects”).
Viral reactivation cases of hepatitis B reactivation have been reported in patients receiving CALQUENCE. Hepatitis B virus (HBV) status should be established before initiating treatment with CALQUENCE. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.
Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of CALQUENCE within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected, then appropriate diagnostic evaluations should be undertaken and treatment with CALQUENCE should be suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.
Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Haemorrhage

Serious haemorrhagic events have been reported in patients with haematologic malignancies receiving CALQUENCE monotherapy n=1478 and treated with combination therapy of CALQUENCE with other medicinal products (n=1095), including some with fatal outcome. Major haemorrhage (Grade 3 or higher bleeding events, serious, or any central nervous system events) occurred in 5.5% and 3.5% of patients, respectively, with fatalities occurring in 0.1% and 0.1% of patients, respectively. The most common major haemorrhage events were gastrointestinal haemorrhage (1.4% and 0.7%, respectively) inclusive upper gastrointestinal haemorrhage (0.5% and 0.1%, respectively), haematuria (0.4% and 0.5%, respectively), haematoma (0.5% and 0.2%, respectively), epistaxis (0.3% and 0%, respectively), intracranial haemorrhage (1.1% and 0.5%, respectively) inclusive subdural haematoma (0.3%, and 0.2%, respectively), and retinal haemorrhage, (0.3% and 0.3%, respectively). Overall, bleeding events (all grades), including bruising and petechiae, occurred in 46.1% and 36.1% of patients, respectively.
The mechanism for the bleeding events is not well understood.
Warfarin or other vitamin K antagonists should not be co-administered with CALQUENCE.

Patients receiving antithrombotic agents may be at increased risk of haemorrhage. Use caution with antithrombotic agents. Additional monitoring of patients for signs and symptoms of bleeding is necessary when concomitant use is medically necessary.
Based on a benefit-risk assessment, CALQUENCE should not be administered for at least 3 days pre- and post-surgery.

Cytopenias

Cytopenias have occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy (n=1478) and treated with combination therapy of CALQUENCE with other medicinal products (n=1095). Overall frequencies for neutropenia were 19.4% and 44.7%%, respectively, for anaemia 17.1% and 12.6%, respectively and for thrombocytopenia 11.5% and 14.2%, respectively. Treatment-emergent Grade ≥3 cytopenias occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy and treated with combination therapy of CALQUENCE with other medicinal products, including neutropenia (17.5% and 40.5%, respectively), anaemia (9.5% and 5.6%, respectively) and thrombocytopenia (6.2% and 7.4%, respectively) based on laboratory measurements.
Monitor complete blood counts as medically appropriate.

Atrial Fibrillation

In patients with haematologic malignancies (n=1478) treated with CALQUENCE monotherapy, atrial fibrillation/flutter of any grade occurred in 7.4% of patients and Grade 3 or higher atrial fibrillation/flutter occurred in 2.3% of patients. In patients treated with combination therapy of CALQUENCE with other medicinal products (n=1095), atrial fibrillation/flutter of any grade occurred in 4.1% of patients and Grade 3 or higher atrial fibrillation/flutter occurred in 1.7% of patients. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as appropriate.

Tumor Lysis Syndrome (TLS)

Tumour lysis syndrome has been reported with acalabrutinib therapy. Patients with high tumour burden prior to treatment are at risk of tumour lysis syndrome. Monitor patients closely and take appropriate precautions.

Hepatotoxicity, including drug-induced liver injury (DILI)

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including CALQUENCE. Evaluate bilirubin and transaminases at baseline and throughout treatment with CALQUENCE.

For patients who develop abnormal liver tests after CALQUENCE, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold CALQUENCE. Upon confirmation of DILI, discontinue CALQUENCE.

Potential at-risk populations that have not been investigated

Patients with central nervous system (CNS) lymphoma or leukemia; known prolymphocytic leukemia or history of or currently suspected Richter's syndrome; Significant cardiovascular disease; uncontrolled active systemic fungal, bacterial, viral, or other infection, including active hepatitis B or C infection, and known history of infection with human immunodeficiency virus (HIV); drug-induced pneumonitis; history of stroke or intracranial hemorrhage within 6 months before first dose of study drug; history of bleeding diathesis; anticoagulation with warfarin or equivalent vitamin K antagonists; treatment with proton-pump inhibitors or requiring steroids at daily doses >20 mg prednisone equivalent systemic exposure daily have been excluded from the clinical trials.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e. is essentially «sodium-free».

Interactions

Active Substances that may increase acalabrutinib plasma concentrations

CYP3A Inhibitors

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.9-fold and 5.1-fold in healthy subjects (N=17), respectively.
Concomitant use with strong CYP3A/P-gp inhibitors should be avoided. If the strong CYP3A/P-gp inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, treatment with Calquence should be interrupted see "Dosage/Administration"). Co-administration with moderate CYP3A inhibitors (400 mg fluconazole as single dose or 200 mg isavuconazole as repeated dose for 5 days) in healthy subjects increased acalabrutinib Cmax and AUC by 1.4-fold to 2-fold while the active metabolite ACP-5862 Cmax and AUC was decreased by 0.65-fold to 0.88-fold relative to when acalabrutinib was dosed alone. No dose adjustment is required in combination with moderate CYP3A inhibitors. Monitor patients closely for adverse reactions (see "Dosage/Administration").

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A Inducers

Co-administration of a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77% in healthy subjects (N=24), respectively.

Gastric Acid Reducing Medications

No clinically significant differences in acalabrutinib pharmacokinetics were observed when used concomitantly with rabeprazole, a proton pump inhibitor. Acalabrutinib tablets can be co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids).

Effect of Aclabrutinib and its active metabolite, ACP-5862 on the metabolism of other substances

In vitro, acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, UGT1A1, and UGT2B7. ACP-5862 is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6, CYP3A4/5, UGT1A1, and UGT2B7 *in vitro*. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4 mRNA; ACP-5862 weakly induces CYP3A4.

CYP3A Substrates

Based on in vitro and clinical data, and PBPK modelling, no interaction with CYP3A4 substrates is expected at the clinically relevant concentrations (see section “Properties/Effects”).

Effects of Acalabrutinib and its active metabolite, ACP-5862, on Drug Transport Systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP (see section “Pharmacokinetics”).
ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

Interactions with transport proteins

In vitro, acalabrutinib and its active metabolite, ACP-5862, are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3, *in vitro*. ACP-5862 is not a substrate of OATP1B1 or OATP1B3.
Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and MATE2-K at clinically relevant concentrations.

Pregnancy, lactation

Pregnancy

There are insufficient clinical data on CALQUENCE use in pregnant women. Based on findings from animal studies, there may be a risk to the foetus and an dysfunctional labor (dystocia) from exposure to acalabrutinib during pregnancy (see section “Preclinical data”).
CALQUENCE must not be administered during pregnancy unless clearly indicated.
Women of childbearing potential or patients with a partner of childbearing potential should use a very reliable method of contraception during treatment with CALQUENCE and for at least 1 week following

the last dose of CALQUENCE. If a hormonal method of contraception is used, an additional barrier method should also be used.
If the patient becomes pregnant while taking CALQUENCE, the patient must be informed about the potential hazard to the foetus.

Lactation

It is not known whether acalabrutinib or its metabolites are excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed infant or on milk production. Acalabrutinib and its active metabolite were excreted in rat milk (see «Preclinical data»).A risk to the suckling child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with CALQUENCE and for 2 weeks after receiving the last dose.

Fertility

There are no data on the effect of CALQUENCE on human fertility. In a nonclinical study of acalabrutinib in male and female rats, no adverse effects on fertility parameters were observed (see section “Preclinical Data”).

Effects on ability to drive and use machines

The influence of Acalabrutinib on the ability to drive and use machines has not been studied. As during treatment with acalabrutinib the events of headache, fatigue, dizziness, falls and syncopes have been reported, patients who experience these symptoms should be advised not to drive or use machines until symptoms abate. Patients should be made aware of the possible occurrence of these effects (see section “Undesirable effects”).

Undesirable effects

The overall safety profile of acalabrutinib is based on pooled data from 1478 patients with haematologic malignancies receiving acalabrutinib as monotherapy and pooled data from 1095 patients treated with the combination of acalabrutinib and either obinutuzumab (n=223 patients), bendamustine and rituximab (n=297 patients), venetoclax (n=291 patients), or ventoclax and obinutuzumab (n=284 patients). The median duration of treatment with CALQUENCE was 28.2 months for monotherapy and 49.7 months for combination therapy. The median duration of acalabrutinib monotherapy treatment across the pooled dataset was 38.2 months.

CALQUENCE monotherapy

In the 1478 patients treated with CALQUENCE monotherapy, the most commonly (≥ 10%) reported adverse reactions of any grade were haemoglobin decreased (47.4%), absolute neutrophil count decreased (43.9%), platelets decreased (36.9%), diarrhoea (36.7%), headache (36.5%), musculoskeletal pain (31.9%), bruising (30.9%), upper respiratory tract infection (25.8%), cough (25.2%), arthralgia (24.0%), fatigue (23.6%), nausea (21.8%), leukopenia (20.8%),rash (20.3%),

contusion (20.2%), neutropenia (19.4%), second primary tumour (17.6%), anaemia (17.1%), dizziness/lightheadedness (17.9%), bleeding / haematoma (16.3%), pneumonia (15.8 %), constipation (15.2%), abdominal pain (14.5%), vomiting (14.0%), thrombocytopenia (11.5%), sinusitis (11.4%) and hypertension (11.2%).
The most commonly (≥5%) reported Grade ≥ 3 adverse reactions were absolute neutrophil count decreased (24.0%), leukopenia (18.2%), neutropenia (17.5%), haemoglobin decreased (10.8%), platelets decreased (9.5%), anaemia (9.5%), pneumonia (8.7%), second primary malignancy (6.7%), thrombocytopenia (6.2%) and SPM excluding non-melanoma skin (5.5%).
The most common serious adverse reactions (≥1%), which also included fatal events, were infections including pneumonia (8.3%) and sepsis (2.8%) second primary tumours (7.1%), as well as haemorrhage / haematoma (2.8%), leukopenia (2.2%), neutropenia (2.2%) and anaemia (2.7%). The infections predominantly occurred in the absence of Grade 3 or 4 neutropenia (see section “Warnings and Precautions”).
Dose reductions due to adverse events were reported in 5.9% of patients. Discontinuation due to adverse events was reported in 15.8% of the patients with the most common events leading to discontinuation being pneumonia (0.8%), COVID-19 (0.6%), COVID-19 pneumonia (0.5%) and thrombocytopenia (0.4%). The adverse drug reactions for patients receiving acalabrutinib monotherapy are listed in Table 4.

Calquence combination therapy

In the 1095°patients receiving treatment with CALQUENCE as combination therapy, the most commonly (≥10%) reported adverse drug reactions of any grade were absolute neutrophil count decreased (75.1%), platelets decreased (54.2%), haemoglobin decreased (52.8%), leukopenia (46.5%), neutropenia (44.7%), diarrhoea (38.3%), headache (33.7%), musculoskeletal pain (32.1%), nausea (27.5%), rash (24.7%), bruising (23.9%), fatigue (22.5%), arthralgia (19.5%), cough (18.0%), contusion (17.4%), upper respiratory tract infection (16.5%), constipation (15.4%), vomiting (15.0%), thrombocytopenia (14.2%), dizziness / vertigo (15.3%), haemorrhage / haematoma (13.6%), anemia (12.6%), second primary malignancy (12.1%), and abdominal pain (11.8%).
The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were absolute neutrophil count decreased (47.0%), leukopenia (41.9%), neutropenia (40.5%), platelets decreased (12.3%), haemoglobin decreased (7.7%), thrombocytopenia (7.4%), anemia (5.6%), and pneumonia (5.2%).
In pooled analyses of patients treated with the combination of acalabrutinib plus obinutuzumab (n=223), a higher overall frequency of the following adverse reactions was observed, compared to patients receiving monotherapy with acalabrutinib (n=1040): infections (74 vs 66.7%) including Grade ≥3 infections (21.5 vs 17.6%), upper respiratory tract (31.4 vs 22%) and other very common infections, musculoskeletal and connective tissue disorders (58.3 vs 51.6%) primarily driven by arthralgia (26.9 vs 19.1%) and pain in extremity (13.9 vs 8.9%), fatigue (30.5 vs 21.3%), contusion (27.4 vs 21.7%), dizziness (23.8 vs 13.4%) and falls (14.8 vs 7.9%). The overall frequency of ≥Grade

3 AE (70.4 vs 54.1%) was also increased in combination pool vs monotherapy pool and was primarily driven by higher incidence of Grade ≥3 neutropenia (23.8 vs 11.2%). In addition, higher rates with ≥10% PT differences of neutropenia (25.1 vs 12.3%), infusion related reactions (19.3 vs 0.8%) and maculo-papular rash (17 vs 4.9%) were observed.

The ADRs identified in clinical studies with patients receiving Acalabrutinib monotherapy versus combination therapy with acalabrutinib and other medicinal products are described in Table°5. Adverse drug reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are sorted by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: very common (≥1/10); common (>1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 5. Adverse drug reactions* of Patients with Haematological Malignancies treated with acalabrutinib monotherapy (n= 1478) or as combination therapy with other medicinal products (n=1095).

MedDRA SOC	**MedDRA Term**	**CIOMS descriptor/ Overall Frequencyall CTCAE-Grades [Frequency of CTCAE Grade ≥3]†**	
		Monotherapy	**Combination therapy**
Infections and Infestations	Upper respiratory tract infection	Very common (25.8%) [1.2%]	Very common (16.5%) [0.6%]
	COVID-19	Common (7.4) [2.0%]	Very common (22.7%) [6.3%]
	COVID-19 pneumonia	Common (2.0) [1.9%]	Very common (10.4%) [9%]
	Sinusitis	Very common (11.4%) [0.4%]	Very common (6.7%) [0.2%]
	Pneumonia	Very common (15.8%) [8.7%]	Common (9.7%) [5.2%]
	Urinary tract infection	Common (9.9%) [1.8%]	Very common (9.0%) [0.8%]
	Nasopharyngitis	Common (8.3%) [0%]	Common (5.6%) [0.1%]
	Bronchitis	Common (9.7%) [0.6%]	Common (5.8%) [0.3%]
	Herpes viral infections[1]	Common (8.9%) [0.9%]	Common (7.8%) [0.7%]
	Sepsis[1]	Common (3.2%) [3.0%]	Common (2.6%) [2.6%]

	Aspergillus infections[1]	Uncommon (0.3%) [0.2%]	Very rare (0.2%) [0.2%]
	Hepatitis B reactivation	Uncommon (0.4%) [0.3%]	Uncommon (0.5%) [0.1%]
Neoplasms benign, malignant and unspecified[6]	Second Primary Malignancy[2]	Very common (17.6%) [6.7%]	Very common (12.1%) [4.7%]
	SPM excluding non-melanoma skin[3]	Common (9.7%) [5.5%]	Common (6.8%) [3.7%]
	Non-Melanoma Skin Malignancy	Common (9.9%) [1.4%]	Common (7.2%) [1.2%]
Blood and lymphatic system disorders	Neutropenia[1]	Very common (19.4%) [17.5%]	Very common (44.7%) [40.5%]
	Anemia[1]	Very common (17.1%) [9.5%]	Very common (12.6%) [5.6%]
	Thrombocytopenia[1]	Very common (11.5%) [6.2%]	Very common (14.2%) [7.4%]
	Leukopenia[1]	Very common (20.8%) [18.2%]	Very common (46.5%) [41.9%]
	Lymphocytosis	Uncommon (0.5%) [0.3%]	Uncommon (0.5%) [0.2%]
	Absolute neutrophil count decreased[7]	Very common (43.9%) [24.0%]	Very common (75.1%) [47.0%]
	Haemoglobin decreased[7]	Very common (47.4%) [10.8%]	Very common (52.8%) [7.7%]
	Platelets decreased[7]	Very common (36.9%) [9.5%]	Very common (54.2%) [12.3%]
Metabolism and nutrition disorders	Tumour Lysis Syndrome	Uncommon (0.5 %) [0.4%]	Uncommon (0.9%) [0.9%]
Nervous system disorders	Headache	Very common (36.5%) [1.2%]	Very common (33.7%) [1.1%]
	Dizziness / Vertigo[1]	Very common (17.9%) [0.3%]	Very common (15.3%) [0.5%]
Cardiac disorders	Atrial Fibrillation/Flutter[4]	Common (7.4%) [2.3%]	Common (4.1%) [1.7%]
Vascular disorders	Bruising[1]	Very common (30.9%) [0%]	Very common (23.9%) [0.1%]
	Contusion	Very common (20.2%) [0%]	Very common (17.4%) [0%]

	Petechiae	Common (8.9%) [0%]	Common (5.6%) [0%]
	Ecchymoses	Common (5.7%) [0%]	Common (3.2%) [0.1%]
	Haemorrhage / haematoma[1]	Very common (16.3%) [3.2%]	Very common (13.6%) [1.6%]
	Gastrointestinal haemorrhage	Uncommon (0.6%) [0.5%]	Uncommon (0.3%) [0.3%]
	Intracranial haemorrhage	Uncommon (0.3%) [0.2%]	Uncommon (0%) [0%]
	Epistaxis	Common (8.0 %) [0.3%]	Common (4.6%) [0%]
	Hypertension	Very common (11.2%) [4.7%]	Common (8.8%) [3.8%]
Respiratory, thoracic and mediastinal disorders	Cough	Very common (25.2%) [0.4%]	Very common (18.0%) [0.3%]
Gastrointestinal disorders	Diarrhoea	Very common (36.7%) [2.6%]	Very common (38.3%) [3.0%]
	Nausea	Very common (21.8%) [0.8%]	Very common (27.5%) [0.5%]
	Constipation	Very common (15.2%) [0.1%]	Very common (15.4%) [0.4%]
	Abdominal pain[1]	Very common (14.5%) [1.2%]	Very common (11.8%) [1.5%]
	Vomiting	Very common (14.0%) [0.7%]	Very common (15.0%) [0.5%]
Skin and subcutaneous tissue disorders	Rash[1]	Very common (20.3%) [0.9%]	Very common (24.7%) [3.4%]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[5]	Very common (31.9%) [1.8%]	Very common (32.1%) [2.0%]
	Arthralgia	Very common (24.0%) [0.9%]	Very common (19.5%) [1.0%]

General disorders and administration site conditions	Fatigue	Very common (23.6%) [2.0%]	Very common (22.5%) [1.3%]
	Asthenia	Common (7.0%) [0.9%]	Common (6.7%) [0.4%]

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[1] Includes multiple ADR terms.

[2] Second primary malignancies were defined by SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non-haemoatological malignant tumours SMQ), SMQ Malignant lymphomas [narrow], and SMQ Myelodysplastic syndrome [narrow]).

[3] Second primary malignancies (excl non-melanoma skin) were defined by the criteria for second primary malignancies excluding PTs mapping to High Level Term Skin neoplasms malignant and unspecified (excl melanoma).

[4] Includes any PT containing atrial fibrillation or atrial flutter.

[5] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myofascial pain syndrome, neck pain, pain in extremity, myalgia, spinal pain

[6] Includes events beyond the end of studies reporting period

[7] Treatment-emergent haematological laboratory abnormalities

Description of specific adverse reactions and additional information

Hepatotoxicity

Hepatotoxicity, predominantly in the form of an increase in transaminases, has been reported in patients receiving Calquence. Severe cases of hepatotoxicity have also been reported. A causal association between Calquence and hepatotoxicity/transaminase elevations has not been established.

Syncope and falls

In clinical trials and in the post-marketing period, syncope and falls have been observed in patients treated with Calquence (see “Effects on ability to drive and operate machinery”).

Elderly patients

Of the 1478 patients in clinical trials of CALQUENCE monotherapy, 42.2% were ≥ 65 years of age and less than 75 years of age and 20.6% were 75 years of age or older. Patients who were 75 years of age or older had higher frequency of Grade ≥3 AE (77.4%) as compared to patients in ≥ 65 years of age and less than 75 years of age group (68.4%) or those less than 65 years of age (59.3%). Higher rates were observed in patients aged 75°years and older compared with the other two age groups for any-grade pneumonia (19.7%, 15.9% and 13.5%, respectively), including Grade ≥3 pneumonia (14.4%, 8.2% and 6.0%, respectively).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for acalabrutinib overdose and symptoms of overdose have not been established. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

Properties/Effects

ATC code

L01EL02

Mechanism of action

Acalabrutinib is a selective small-molecule inhibitor of Bruton tyrosine kinase (BTK). BTK is a signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis.
Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK (IC_{50} ≤ 5 nM) with minimal off-target interactions. In a screen of 380 mammalian wild-type kinases, the only additional kinase interactions at clinically relevant concentrations of acalabrutinib and ACP-5862 were with BMX and ERBB4, with 3- to 4-fold less potency than BTK.
In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69, inhibited malignant B-cell proliferation and survival, and had minimal activity on other immune cells (T cells and NK cells).

Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg twice daily, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology

In a dedicated QT study, at a dose 4 times the maximum recommended dose, CALQUENCE does not prolong the QT/QTc interval to any clinically relevant extent (e.g., not greater than or equal to 10 ms).

Clinical efficacy

Patients with Previously Untreated CLL – ELEVATE-TN

The safety and efficacy of CALQUENCE in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. The CLL had to be CD20+, diagnosed according to IWCLL 2008 criteria and active/needing treatment. Furthermore, absolute neutrophil count and platelets had to be independent of growth factor or transfusion support and had

to be above 750 and 50,000 cells/μL, respectively (in case of bone marrow involvement above 500 and 30,000 cells/μL, respectively). Patients with CNS involvement, prolymphocytic leukemia or Richter syndrome were excluded from participation. Patients received CALQUENCE plus obinutuzumab, CALQUENCE monotherapy, or obinutuzumab plus chlorambucil. Patients 65 years of age or older or between 18 and 65 years of age with coexisting medical conditions (creatinine clearance 30-69 mL/min and/or CIRS-G score > 6) were included in ELEVATE-TN. The trial also allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

Patients were randomised in a 1:1:1 ratio into 3 arms to receive

- CALQUENCE plus obinutuzumab (CALQUENCE+G): CALQUENCE 100 mg was administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.
- CALQUENCE monotherapy: CALQUENCE 100 mg was administered twice daily until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was 28 days.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and geographic region (North America and Western Europe versus Other). After confirmed disease progression, 45 patients randomised on the GClb arm crossed over to CALQUENCE monotherapy.

The baseline characteristics were generally balanced in the three arms (Calquence plus obinutuzumab [n=179], Calquence monotherapy [n=179] and obinutuzumab plus chlorambucil [n=177]): median age 70, 70 and 71 years, respectively; 62%, 62% and 59.9% were male, respectively; 94.4%, 92.2% and 94.4% had an ECOG performance status of 0-1, respectively; the median time from diagnosis was 30.5, 24.4 and 30.7 months, respectively; cytogenetic factors (del17p, del11q, TP53 mutation, unmutated IGHV, complex karyotype) as well as Rai stage were all generally balanced.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 28.3 months, PFS by IRC indicated a 90% statistically significant reduction in

the risk of disease progression or death for previously untreated CLL patients in the CALQUENCE+G arm compared to the GClb arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 37 deaths: 9 (5%) in the CALQUENCE+G arm, 11 (6.1%) in the CALQUENCE monotherapy arm, and 17 (9.6%) in the GClb arm. Efficacy results are presented in Table 6.

Table 6. Efficacy Results in (ELEVATE-TN) Patients with CLL

Characteristic	**CALQUENCE plus Obinutuzumab N=179**	**CALQUENCE-Monotherapy n=179**	**Obinutuzumab plus Chlorambucil n=177**
Progression-Free Survival *			
Number of events (%)	14 (7.8)	26 (14.5)	93 (52.5)
Median (95%-KI), months	n.e.	n.e. (34.2; n.e.)	22.6 (20.2; 27.6)
HR† (95%-KI)	0.10 (0.06; 0.17)	0.20 (0.13; 0.30)	-
Overall Response Rate *			
ORR, n (%) (95%-KI)	168 (93.9) (89.3; 96.5)	153 (85.5) (79.6; 89.9)	139 (78.5) (71.9; 83.9)
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response

* Per IRC assessment

† Based on stratified Cox-Proportional-Hazards model

PFS results for CALQUENCE with or without obinutuzumab were consistent across subgroups, including high risk features (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV).. Richter's transformation was reported for 6 patients (3.4%) in the acalabrutinib monotherapy arm (no patients in the combination therapy arm) during the randomized period and for 1 patient (2.2%) in the chlorambucil / obinutuzumab arm during the crossover period.

Patients with Previously Untreated CLL– Fixed duration therapy - AMPLIFY

The safety and efficacy of CALQUENCE in combination with venetoclax in previously untreated CLL was analyzed in a randomised, multi-centre, open-label Phase 3 study (AMPLIFY). Patients received CALQUENCE plus venetoclax, or Investigator's choice of chemoimmunotherapy, either FCR (fludarabine plus cyclophosphamide plus rituximab) or BR (bendamustine plus rituximab). AMPLIFY included patients previously untreated for CLL without del(17p) or TP53 mutation that were 18 years of age and older. Patients with an individual CIRS-G score of 4 or a total CIRS-G score >6, uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura, history of confirmed progressive multifocal leukoenphalopathy and have received a live virus vaccination within 28 days of first study drug dose were excluded from participation. The trial also allowed patients to

receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists. The study enrolled patients during the COVID-19 pandemic.
Patients were randomised in a 1:1 ratio into arms to receive:

- CALQUENCE plus venetoclax (AV): CALQUENCE 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1 patients started the venetoclax 5week dose titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Each cycle was 28 days.

- Investigator's choice of chemoimmunotherapy (FCR/BR):
    - Fludarabine plus cyclophosphamyde plus rituximab (FCR): Fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) were administered on Days 1-3 up to a maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on Day 1 Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.
    - Bendamustine plus rituximab (BR): Bendamustine 90 mg/m^2 was administered on Days 1 and 2 up to maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on Day 1 Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.

Patients were stratified by age (>65 years or ≤65), IGHV mutational status (mutated versus unmutated), Rai stage (high risk [≥3] versus non-high risk) and geographic region (North America versus Western Europe versus other). Table 7 summarises the baseline demographics and disease characteristics of thetreatment arms.

Table 7. Baseline Patient Characteristics in (AMPLIFY) Patients with Previously Untreated CLL

Characteristic	**AV N=291**	**FCR/BR N=290**
Age, years; median (range)	61 (31-84)	61 (26-86)
Male; %	61.2	63.1
Caucasian; %	91.1	86.9
ECOG performance status 0-1; %	90.0	90.3
Median time from diagnosis to randomization (months)	28.5	29.6
Bulky disease with nodes ≥ 5 cm; %	38.8	42.8
Cytogenetics/FISH Category; %		
11q deletion	17.5	15.9
Complex karyotype (≥ 3 abnormalities)	15.5	14.5
Unmutated IGHV; %	57.4	59.3
Rai stage; %		
0	1.0	1.4
I	16.2	21.4
II	35.7	33.4
III	23.7	20.3

IV	23.4	23.4

The primary endpoint was IRC-assessed PFS for AV versus Investigator's choice of chemoimmunotherapy (FCR/BR) arm as assessed by IWCLL 2018 criteria. Additional efficacy endpoints were the minimal residual disease (MRD) in the peripheral blood by flow cytometry (10^{-4}) and overall survival (OS). MRD comparison was based on Cycle 9 (AV), or 12 weeks after the start of Cycle 6 (FCR/BR).
With a median follow-up of 41.3 months, IRC-assessed PFS indicated a 35% statistically significant reduction in risk of disease progression or death (Hazard Ration (HR) 0.65 (95%-KI 0,49; 0,87) in patients treated with AV compared to FCR/BR.
A negative MRD at the above-mentioned time points was achieved in 78 (26.8%) of patients treated with AV and 148 (51.0%) patients in FCR/BR arm C (relative risk in favour of the FCR/BR arm: 0.5 (95% CI 0.4; 0.7).
After a median follow-up period of 46.4 months, the OS HR was 0.42 [95% CI (0.25, 0.70)] for AV arm compared to the FCR/BR arm, with a total of 67 death events; 23 (7.9%) in AV arm and 44 (15.2%) in FCR/BR arm. As the statistical test procedure could not be continued due to the MRD result, no statistical significance could be determined for the OS result.
The benefit of CALQUENCE in combination with venetoclax on PFS risk reduction was consistent, in CLL patients (unmutated IGHV).

Patients with CLL who received at least one prior therapy - ASCEND

The safety and efficacy of CALQUENCE in relapsed or refractory CLL were evaluated in a randomised, multi-centre, open-label phase 3 study (ASCEND) of 310 patients who received at least one prior therapy. Prior treatment with a B-cell lymphoma (BCL)-2 inhibitor (e.g. Venetoclax), a B-cell receptor (BCR) inhibitor (e.g. BTK or PI3K inhibitors) or radio- or toxin-conjugated antibody therapy was not permitted. The CLL had to be CD20+, diagnosed according to IWCLL 2008 criteria and active/needing treatment. Furthermore, absolute neutrophil count and platelets had to be independent of growth factor or transfusion support and had to be above 750 and 50,000 cells/µL, respectively (in case of bone marrow involvement above 500 and 30,000 cells/µL, respectively). Patients with CNS involvement, prolymphocytic leukemia or Richter syndrome were excluded from participation. Patients received CALQUENCE monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The trial allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.
Patients were randomised 1:1 to receive either:

- CALQUENCE 100 mg twice daily until disease progression or unacceptable toxicity, or
- Investigator's choice:

- Idelalisib 150 mg twice daily until disease progression or unacceptable toxicity in combination with ≤ 8 infusions of rituximab (375 mg/m2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles
- Bendamustine 70 mg/m^2 (Day 1 and 2 of each 28-day cycle) in combination with rituximab (375 mg/m^2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and number of prior therapies (1 to 3 versus ≥ 4). After confirmed disease progression, 35 patients randomised on investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab crossed over to CALQUENCE.

The baseline characteristics were generally balanced in the two arms (Calquence montherapy [n=155]): median age 68 and 67 years, respectively; 69.7% and 64.5% were male, respectively; 87.7% and 86.5% had an ECOG performance status of 0-1, respectively; the median time from diagnosis was 85.3 and 79 months, respectively; the median time since last prior CLL therapy to first dose was 26.4 and 22.7 months, respectively; cytogenetic factors (del17p, del11q, TP53 mutation, unmutated IGHV, complex karyotype) as well as Rai stage were all generally balanced.

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). At the time of the first pre-specified analysis with a median follow-up of 16.1 months, CALQUENCE demonstrated a clinically meaningful and statistically significant improvement in IRC-assessed PFS compared with IR/BR (hazard ratio 0.31 [95% CI, 0.20 to 0.49] P < 0.0001)]. At the time of analysis, median overall survival had not been reached in any arm with a total of 33 deaths: 15 (9.7%) in the CALQUENCE monotherapy arm and 18 (11.6%) in the investiator's choice of either idelalisib plus rituximab or bendamustine plus rituximab arm. In a further not pre-specified analysis after a median follow-up period of 22 months, the median PFS, which in contrast to the primary endpoint as assessed by the investigator, was not achieved in the Calquence arm and was 16.8 months in the IR/BR arm (hazard ratio 0.27 [95% KI 0.18 to 0.40]). The data on overall survival remained immature with 21 (13.5%) and 26 (16.8%) events in the Calquence and comparator arm, respectively. Efficacy results of the pre-specified analysis are presented in Table 8.

Table 8. Efficacy Results in (ASCEND) Patients with CLL

	CALQUENCE Monotherapy n=155	**Investigator's choice of idelalisib + rituximab (n=119) or bendamustine + rituximab (n=36) n=155**
Progression-Free Survival *		
Number of events (%)	27 (17.4)	68 (43.9)
Median (95%-KI), months	n.e.	16.5 (14.0; 17.1)

HR† (95%-KI)	0.31 (0.20; 0.49)	
Overall Response Rate *		
ORR, n (%) (95%-KI)	126 (81,3) (74.4; 86.6)	117 (75.5) (68.1; 81.6)
CR, n (%)	0	2 (1.3)
Dauer des Ansprechens (DoR)		
Median (95%-KI), months	n.e.	13.6 (11.9; n.e.)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; PR=partial response

* Per IRC assessment

† Based on stratified Cox-Proportional-Hazards model

PFS results for CALQUENCE were consistent across subgroups, including high risk features (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV).

Richter's transformation was reported for 4 patients (2.6%) in the acalabrutinib monotherapy arm and for 3 patients (2.0%) in the idelalisib plus rituximab / bendamustine plus rituximab arm during the randomized period, and for 2 patients (5.7%) in the idelalisib plus rituximab / bendamustine plus rituximab arm during the crossover period.

Patients with previously untreated MCL - ECHO

The efficacy of CALQUENCE in patients with previously untreated MCL was evaluated in ECHO, a randomised, double-blind, placebo controlled, multicentre phase 3 study. ECHO included 598 patients 65 years of age and older with confirmed MCL that was previously untreated. Patients with the goal of tumour reduction before stem cell transplant were excluded.

Patient randomisation was stratified by geographic region (North America versus Western Europe versus Other) and simplified MIPI (Mantle Cell Lymphoma International Prognostic Index) score (0-3 versus 4-5 versus 6-11). The study enrolled patients during the COVID-19 pandemic.

Patients were randomised in 1:1 ratio in 2 arms to receive:

- Calquence plus bendamustine and rituximab (Calquence + BR) arm - Calquence 100 mg was administered twice daily from Day 1 of Cycle 1, continuously. Bendamustine, 90 mg/m^2, was intravenously administered over 30 minutes on Days 1 and 2 of each of six 28-day cycles; and rituximab, 375 mg/m^2, was intravenously administered on Day 1 of each cycle of six 28-day cycles. Calquence + BR was administered for a maximum of 6 treatment cycles (induction treatment).
- Placebo plus bendamustine and rituximab (Placebo + BR) arm – Placebo was administered twice daily from Day 1 of Cycle 1, continuously. Bendamustine, 90 mg/m^2, was intravenously administered over 30 minutes on Days 1 and 2 of each of six 28-day cycles; and rituximab, 375 mg/m^2, was intravenously administered on Day 1 of each cycle of six 28-day cycles. Placebo + BR was administered for a maximum of 6 treatment cycles (induction treatment).

CALQUENCE or placebo was administered continuously until disease progression or unacceptable toxicity. After the induction treatment, patients in the placebo + BR arm that were achieving a response (PR or CR) received rituximab maintenance at 375 mg/m^2 on Day 1 of every other cycle for maximum of 12 additional doses up to Cycle 30. Patients randomised to placebo + BR arm, who had confirmed PD were eligible to cross over to CALQUENCE monotherapy at 100 mg twice daily dose until their second disease progression or unacceptable toxicity.

The median age was 71 years (65-86), 70.7% were males, 78.3% were White, 93.1% had an ECOG performance status of 0-1. The simplified MIPI score was low (0-3) in 33.1%, intermediate (4-5) in 42.8% and high (6-11) in 24.1% of patients. A total of 37.7% of patients had tumour bulk ≥ 5 cm and 86% had Ann Arbor stage IV disease. Aggressive variants of MCL such as blastoid and pleomorphic forms were seen in 7.7% and 5.5% of patients respectively. A total of 47.8% patients had Ki-67 score of ≥30%. The baseline characteristics were similar between both treatment arms.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per Lugano Classification for NHL in subjects with previously untreated MCL. Additional multiplicity-adjusted efficacy endpoints were, IRC assessed overall response rate (ORR), and overall survival (OS).

The study design without a second randomization for post-induction therapy does not allow any statement on the benefit of continuous therapy with Calquence until disease progression or unacceptable toxicity.

With a median follow-up of 46.1 months in the CALQUENCE + BR arm and 44.4 months in the Placebo + BR arm, IRC-assessed PFS demonstrated 27% statistically significant reduction in risk of disease progression or death in patients treated with CALQUENCE + BR compared to Placebo + BR. However, inconsistencies were found in certain subgroups, both for PFS and for OS. The inconsistency in relation to gender is particularly notable. The HR for PFS in the 423 men studied was 0.91 (0.68, 1.21) compared to 0.34 (0.19.0.58) in the 175 women, the corresponding HR for OS was 1.01 (0.74, 1.38) for the men and 0.52 (0.28, 0.94) for the women. The ORR assessed by the IRC did not show a statistically significant difference between CALQUENCE + BR and Placebo + BR.

At the time of PFS analysis, median OS had not been reached in any arm with a total of 203 deaths: 97 (32.4%) in the CALQUENCE + BR arm, 106 (35.5%) in the Placebo + BR arm and OS showed no statistically significant difference between treatment arms: HR (95% CI) (stratified) 0.86 (0.65, 1.13).

Efficacy results are presented in Table 9. The Kaplan-Meier curves for PFS are shown in Figure 1.

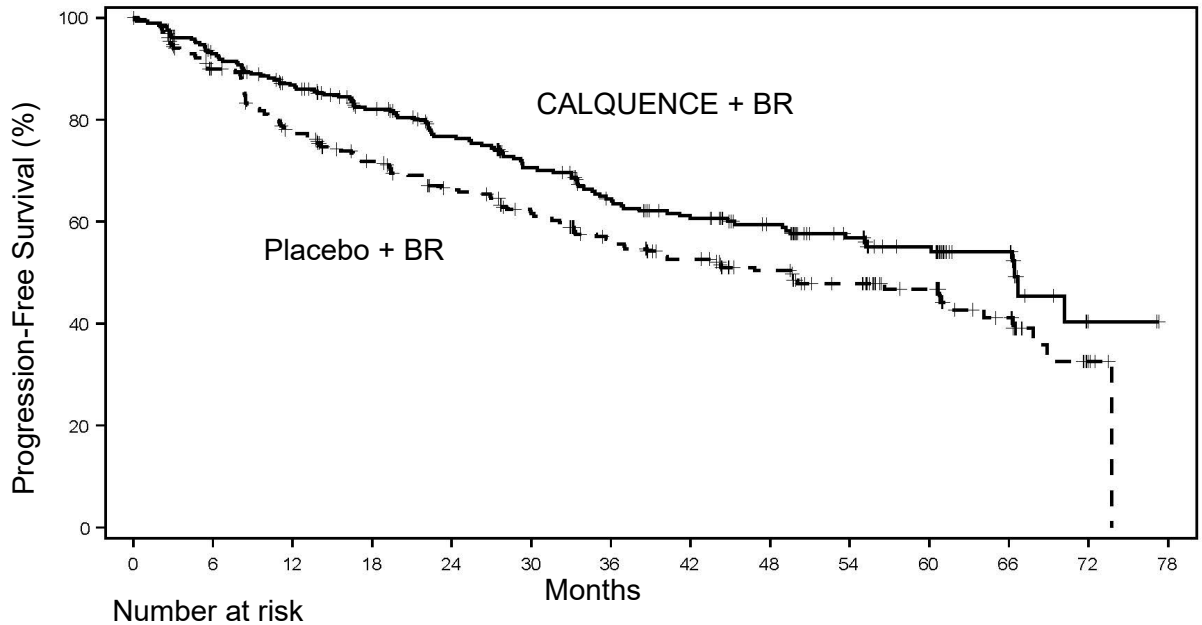
Table 9. Efficacy Results in Patients with previously untreated MCL in ECHO

	CALQUENCE + BR N= 299	**Placebo + BR N= 299**
IRC-assessed PFS		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR (95% CI) (stratified)*	0.73 (0.57, 0.94)	
p-value‡	0.0160	
IRC-assessed ORR		
CR + PR n (%)	272 (91.0)	263 (88.0)

95% CI	87.3,93.8	83.9, 91.3
CR n (%)	199 (66.6)	160 (53.5)
PR n (%)	73 (24.4)	103 (34.4)
ORR difference (vs PBR arm)	3.0%	-
p-value	0.2196	-

HR = hazard ratio, CR = complete response, PR = partial response, NE – not evaluable
* Stratified by randomization stratification factors: Geographic Regions (North American, Western Europe, Other) and simplified MIPI Score (Low risk [0 to 3], Intermediate risk [4 to 5], High Risk [6 to 11]) as collected via IXRS. Estimated based on stratified Cox Proportional Hazards model for hazard ratio (95% CI).
‡ Estimated based on stratified log-rank test for p-value.

Figure 1. Kaplan-Meier Curve of IRC-Assessed PFS in patients with previously untreated MCL (ECHO)



Number at risk

CALQUENCE + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

Patients with MCL who received at least one prior therapy - ACE-LY-004

The safety and efficacy of CALQUENCE in MCL were investigated in an open-label, multicentre, single-arm Phase II study (ACE-LY-004) involving 124 previously treated patients who had not achieved a partial response with prior therapy or who had shown progression after prior therapy. All patients received CALQUENCE 100 mg orally twice daily until disease progression or onset of unacceptable toxicity. The study did not include patients who had previously been treated with BTK inhibitors, other inhibitors of the B-cell receptor signalling pathway (phosphoinositide 3-kinase [PI3K] or SYK) or a BCL-2 inhibitor. The primary endpoint was investigator-assessed overall response rate (ORR) according to the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of response (DoR) was an additional outcome measure. The efficacy results of the primary (12 months) and final (54 months) analyses are presented in Table 10.
In the primary analysis, the median age was 68 (range, 42 to 90) years, 79.8% were male, and 74.2% were white. At study baseline, 92.8% of patients had an ECOG performance status of 0 or 1. The

median time since diagnosis was 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 17.7% with prior stem cell transplantation. The most common previous treatment regimens were CHOP-based (51.6%) and ARA-C (33.9%). At study baseline, 37.1% of patients had at least one tumour with a longest diameter ≥ 5 cm; 72.6% had additional nodal involvement, of whom 50.8% had bone marrow involvement. The simplified MIPI score (which takes into account age, ECOG score, baseline lactate dehydrogenase and leukocyte count) was intermediate in 43.5% of patients and high in 16.9%.

Table 10. Overall response rate and duration of response in (ACE-LY-004) patients with MCL at 12- and 54-month analysis.

	Investigator's assessment after 12 months n=124 n (%) (95% CI*)	**Investigator's assessment after 54 months n=124 n (%) (95% CI*)**
Overall response rate (ORR)		
Overall Response Rate	100 (80.6%) (72.6; 87.2)	101 (81.5%) (73.5; 87.9)
Complete remission	49 (39.5%) (30.9; 48.7)	59 (47.6%) (38.5; 56.7)
Partial remission	51 (41.1%) (32.4; 50.3)	42 (33.9%) (25.6; 42.9)
Stable disease	11 (8.9%) (4.5; 15.3)	10 (8.1%) (3.9; 14.3)
Disease progression	10 (8.1%) (3.9; 14.3)	10 (8.1%) (3.9; 14.3)
Not evaluable†	3 (2.4%) (0.5; 6.9)	3 (2.4%) (0.5; 6.9)
Duration of response (DoR)		
Median (months)	n. r. (13.5; n. r.)	28.6 (17.5; 39.1)

CI = confidence interval; n. r. = not reached
*Exact binomial 95% confidence interval.
†Includes subjects without adequate post-baseline disease assessment.

Pharmacokinetics

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg. Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 is similar across patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including CLL), the geometric mean steady state daily area under the plasma drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) of acalabrutinib were 1679 ng•h/mL and 438 ng/mL, respectively, and for ACP-5862 were 4166 ng•h/mL and 446 ng/mL, respectively.

Absorption

The median time to peak plasma concentrations (T_{max}) was 0.5 (range: 0.2 to 3.0) hours for CALQUENCE, and 0.75 (0.5 to 4.0) hours for ACP-5862. The absolute bioavailability of CALQUENCE was 25%.

Effect of food on acalabrutinib

In healthy subjects, administration of a single 100 mg dose of acalabrutinib with a high fat, high calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 54% and T_{max} was delayed 1-2 hours.

Distribution

Reversible binding to human plasma protein was 97.5% for acalabrutinib and 98.6% for ACP-5862. The *in vitro* mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The mean steady state volume of distribution (V_{ss}) was approximately 34 L for acalabrutinib.

Metabolism

In vitro, acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the arithmetic mean of the terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 1.6 (range: 0.8 to 9.0) hours. The arithmetic mean of $t_{1/2}$ of the active metabolite, ACP-5862, was 6.9 hours (range: 2.5 to 10.1) hours.
The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862. Following administration of a single 100 mg radiolabelled [^{14}C]-acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the faeces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged acalabrutinib in urine and faeces.
Kinetics in specific patient groups

Based on population PK analysis, age, sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Renal impairment

Acalabrutinib undergoes minimal renal elimination. A pharmacokinetic study in patients with renal impairment has not been conducted.

Based on population PK analysis, no clinically relevant PK difference was observed in 408 subjects with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2 as estimated by MDRD), 109 subjects with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2) relative to 192 subjects with normal renal function (eGFR greater than or equal to 90 mL/min/1.73m^2). The pharmacokinetics of acalabrutinib has not been characterised in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical trials (see section “Dosage/Administration”).

Hepatic impairment

Acalabrutinib is metabolized in the liver. In dedicated hepatic impairment studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B), and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant difference was observed between subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST) relative to subjects with normal (n=613) hepatic function (total bilirubin and AST within ULN).

Preclinical data

Repeat dose toxicity

Daily oral administration of acalabrutinib for up to 6 months duration in rats and 9 months in dogs was tolerated at exposure levels that exceed human therapeutic exposures at the recommended dose (1.1-fold in rats, 8.2-fold in dogs, based on AUC).
In rats, renal effects including tubular degeneration were observed at exposures 7 times or greater than that of the recommended human dose. Renal effects were reversible with complete recovery in rats exposed at levels 4.2 times the recommended human dose and partial recovery in rats at the higher exposures (6.8-fold or greater).
In rats, dose-responsive reversible liver findings including individual hepatocyte necrosis were observed after exposures 4.2 times or greater than that of the recommended human dose.
Cardiac toxicities (myocardial haemorrhage, inflammation, necrosis) were observed in rats that died during the study and at exposures equivalent to 6.8 times or greater than that of the human recommended dose. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the maximum tolerated dose (MTD). At exposures representing 4.2 times the human recommended dose, no cardiac toxicities were observed.
Genotoxicity/Mutagenicity

Acalabrutinib was not mutagenic in a bacterial reverse mutation assay, in an *in vitro* chromosome aberration assay, or in an *in vivo* mouse bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Reproductive toxicity

No effects on fertility were observed in male or female rats at exposures 10 or 9 times the human AUC exposure at the recommended dose, respectively.

In a combined fertility and embryofoetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryofoetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma.

In an embryofoetal study in pregnant rabbits, acalabrutinib was administered orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity (doses ≥ 100 mg/kg/day), which were 2.4-times greater than the human exposure levels at the recommended dose.

In a rat reproductive study, dystocia (prolonged /difficult labour) was observed at exposures > 2.3-times the clinical exposure at 100 mg twice daily.

Acalabrutinib and its active metabolite were present in the milk of lactating rats.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store in the original packaging.

Do not store above 30°C.

Keep out of the reach of children.

Authorisation number

68817 (Swissmedic).

Packs

CALQUENCE 100 mg film-coated tablets:
Aluminium/Aluminium blisters. Cartons of 6 x 10 film-coated tablets [A].

Marketing authorisation holder

AstraZeneca AG, 6340 Baar.

Date of revision of the text

July 2025.